DECEMBER 1954

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles by

ROGER BAKER

CURRENT CONCEPTS IN THE MANAGEMENT OF GASTROINTESTINAL DISORDERS

Transcription of a Panel Meeting

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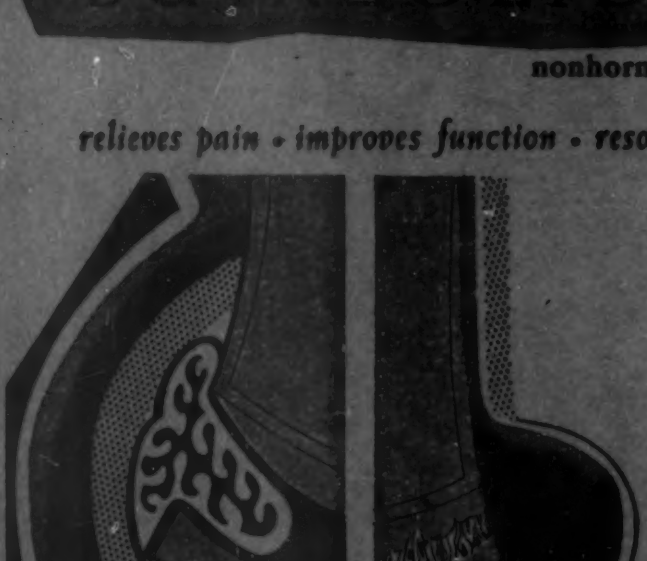

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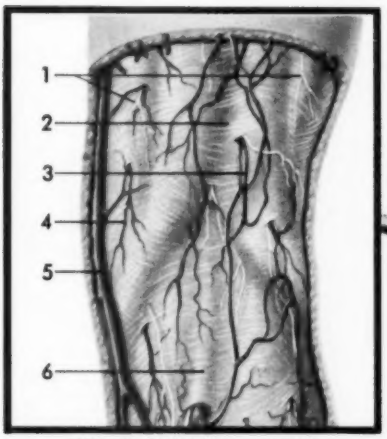
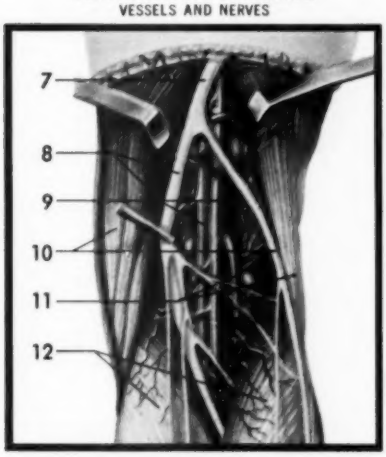
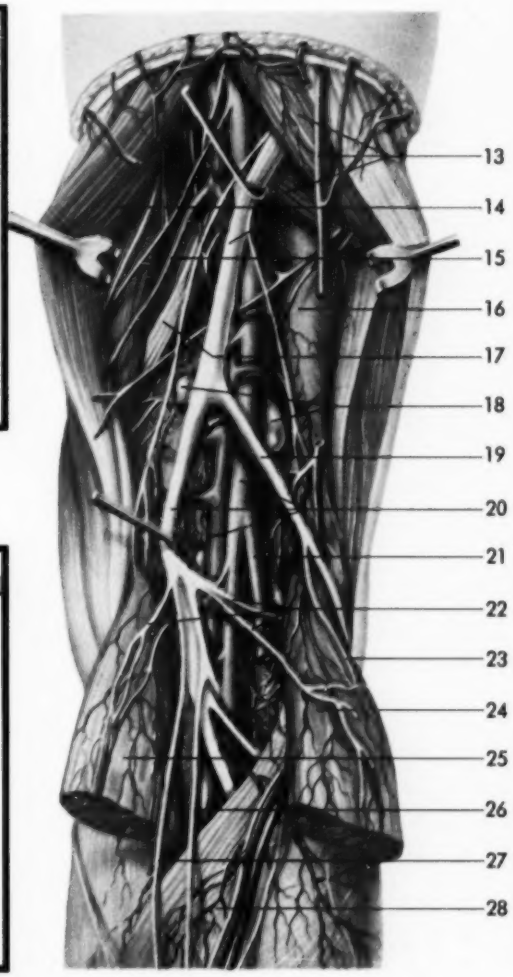


POPLITEAL FASCIA AND SUPERFICIAL VESSELS AND NERVES

DEEPER DISSECTION OF POPLITEAL VESSELS AND NERVES





1 Branches of the posterior femoral cutaneous nerve
2 Popliteal fascia
3 Cutaneous branch of popliteal artery
4 Cutaneous branch of sural artery
5 Great saphenous vein
6 Small saphenous vein (under popliteal fascia)
7 Sciatic nerve
8 Semitendinosus muscle; tibial nerve
9 Popliteal artery and vein
10 Semimembranosus muscle; common peroneal nerve
11 Small saphenous vein; biceps femoris muscle
12 Gastrocnemius muscle
13 Biceps femoris muscle; accessory saphenous vein
14 Semimembranosus muscle; sciatic nerve
15 Muscular branch of popliteal artery
16 Vastus lateralis muscle
17 Adductor magnus muscle
18 Popliteal lymph nodes
19 Common peroneal nerve
20 Tibial nerve; popliteal artery and vein
21 Small saphenous vein
22 Muscular branches of tibial nerve
23 Lateral sural cutaneous nerve
24 Lateral head of gastrocnemius muscle
25 Medial head of gastrocnemius muscle
26 Nerve to soleus muscle
27 Medial sural cutaneous nerve
28 Soleus muscle

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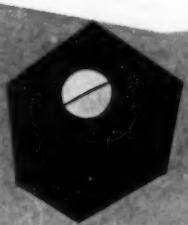

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1. Grayzel, H. G., Heimer, C. B., and Grayzel, R. W.: New York St. J. M. 53:2233, 1953.
2. Sobel, A. E. and Rosenberg, A.: 124th Meeting American Chemical Society, 1953.

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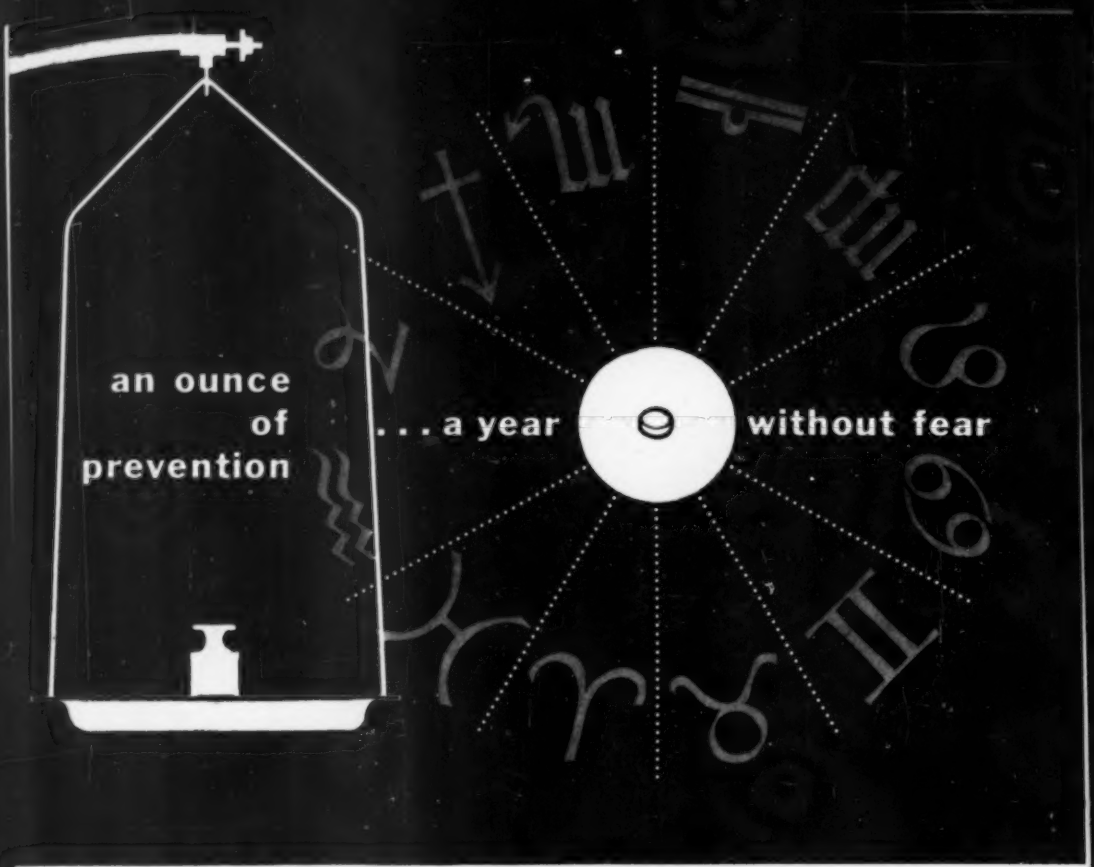

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1. Russek, H. I.; Urbach, K. F.; Doerner, A. A., and Zohman, B. L.: J.A.M.A. *153*:207 (Sept. 19) 1953. 2. Winsor, T., and Humphreys, P.: Angiology *3*:1 (Feb.) 1952. 3. Plotz, M.: New York State J. Med. *52*:2012 (Aug. 15) 1952.

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(1) Kirby, W. M. M.; Waddington, W. S., & Doornink, C. M.: Antibiotics Annual, 1953-1954, New York, Medical Encyclopedia, Inc., 1953, p. 285. (2) Finland, M., & Haight, T. H.: *Arch. Int. Med.* **91**: 143, 1953.

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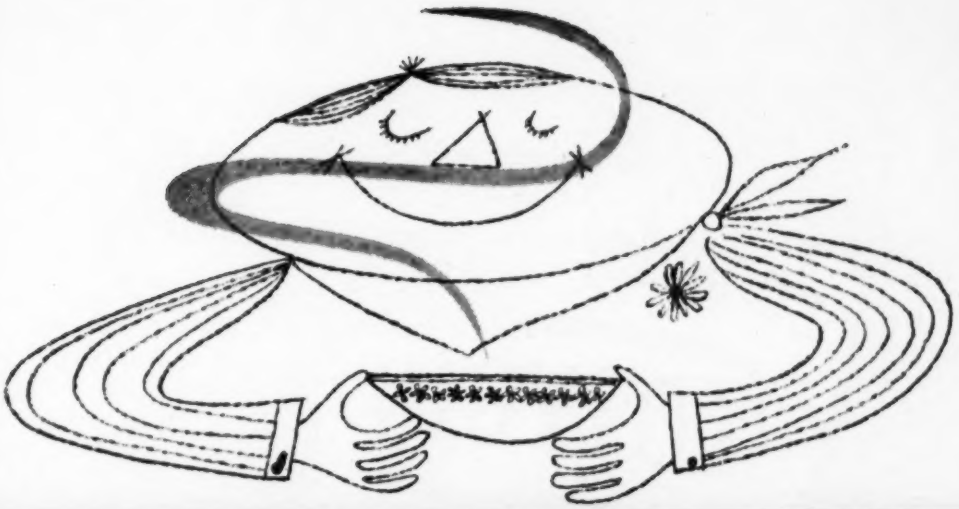

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ROBERT L. CRAIG, *Editor*

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BULLETIN OF
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OF MEDICINE

VOL. 30, NO. 12 DECEMBER 1954

THE INFLUENCE OF CLINICAL AND LABORATORY INVESTIGATION IN ESTABLISHING CURRENT THERAPY OF BLADDER CANCER*

ROGER BAKER

Professor and Director of the Department of Urology, Georgetown University School of Medicine, Washington, D.C.

THE Genito-Urinary Section of The New York Academy of Medicine had its first meeting on December 9, 1890. The first paper was read by Doctor F. R. Sturgis, entitled "The Diagnostic Value of Hematuria in Affections of the Genito-Urinary Organs," which undoubtedly had a direct bearing on our topic this evening. Since that time some of the most significant contributions to the problem of bladder cancer have been made by urologists from the New York scene. To mention only a few, we are all familiar with the work of Buerger, Keyes, Beer, Barringer, McCarthy, Dean, and more recently, the outstanding work of Marshall and Whitmore.

ETIOLOGY

Concerning the cause of bladder cancer little is known, but it is

* Presented by invitation before the Section on Genito-Urinary Surgery of The New York Academy of Medicine, Dec. 16, 1953. Manuscripts received April 1954.
This work supported in part by an American Cancer Society Institutional Grant.

relatively great when compared to the paucity of etiological factors responsible for other major cancers of man. Rehn in 1895 first reported bladder cancer in fuchsin workers. Hueper proved that aniline dye workers have a significantly greater incidence of cancer than in the average population. Experimentally, bladder cancers have been produced by 20-methyl cholanthrene and B-naphthylamine. Acetylaminofluorine and several other azo dyes also selectively produce carcinoma of the bladder. It is interesting at this point to return to history. In 1870, Billroth, the famous Viennese surgeon, contended that "without previous chronic inflammation, cancer does not exist." In 1907, Ribbert stated that cancer originates at the site of local alterations in tissue metabolism. In point of fact, we know that cancer of the bladder has occurred in patients with Hunner ulcers, diverticula, and bladder metaplasia from whatever cause. Leukoplakia of the bladder is considered a premalignant lesion. Benign papillomas of the bladder invariably become malignant if untreated. There is a 2 per cent incidence of malignant degeneration occurring in exstrophy of the bladder. Many patients with bladder cancer have a vesical calculus. In these latter cases the tumor itself is invariably squamous cell and frequently surrounded by marked areas of hyperplasia or metaplasia. Was the hyperplasia or metaplasia first, and the malignant degeneration second, or vice versa? The problem remains unanswered, though speculation is rampant and to say the least, intriguing. In our own laboratory we are concerned to some degree with this phase of bladder cancer. B-naphthylamine fed to dogs produces bladder cancer in a minimum of eleven to twenty-four months. If a foreign body, such as a piece of wood or a calculus, is placed within the dog's bladder or a surgical exstrophy produced, and then B-naphthylamine administered, it appears that the average time for development of cancer is only six to twelve months. In all cases hyperplasia or metaplasia apparently precedes development of the tumors. While we have no evidence that "chronic inflammation" is carcinogenic per se, preliminary evidence indicates that it accelerates the development of bladder cancer in the organism disposed toward tumorigenesis.

Classification of Bladder Tumors

While many different classifications of bladder tumors have been described, covering the range from fibroma to hydatid cyst to fibro-

myxosarcoma, from a practical standpoint three tumors comprise over 97 per cent of those encountered in practice: transitional cell, squamous cell, and adenocarcinoma. The present paper is concerned only with these cellular types. It should also be mentioned that papillomas are not included in this report as these are benign, though premalignant, lesions.

Biopsy: Prior to the investigative work of Jewett and Strong[1] it was common practice to biopsy bladder tumors by means of endoscopic snares or forceps. The contribution of these men and the confirming data of Marshall and others have demonstrated that depth of infiltration is more important in determining therapy and prognosis than grading of the cancer cells. Potentially, cancers that have infiltrated more than midway the bladder muscle will have spread widely and prognosis is extremely poor (about 15 per cent cures) regardless of the accepted method of therapy employed. Potentially, about 85 per cent of patients will be cured, regardless of accepted type of therapy utilized, who have cancers that have penetrated to only the superficial muscle layers or less. Grading of tumor cells affords some indication of rate of growth, but frequently is deceptive. A tumor may be classified as Broder grade one at the surface but be grade three at the base. A grade one or two cancer may have spread through the entire bladder wall and be widely disseminated through lymphatics. On the other hand, a grade four, highly anaplastic cancer may involve only mucosa, submucosa and superficial muscle layers. In the modern treatment of vesical neoplasms, therefore, the endoscopic snares and forceps must be discarded. All patients (even those with benign papilloma) must have transurethral resection of a segment or all of the tumor for biopsy purposes.

Bimanual Examination: Some urologists have stated that bimanual examination is of assistance in determining operability of bladder cancer. Based on observations with some 69 cystectomies, I have been unable to obtain much additional information by this method in the patients in whom such data were most needed. A routine deep transurethral resection biopsy and frequently laparotomy, are the usual procedures, in my experience and that of many others, which are necessary to determine operability and provide a reasonable evaluation of prognosis. Perhaps increasing the number of cases in this series will demonstrate a greater dependence on this highly subjective examination.

Exfoliative Cellular Pathology: In 1892, Ferguson was one of the

first to draw attention to the importance of repeated microscopical examinations of the urine in the diagnosis of bladder tumors. He examined small fragments of tissue in the debris of the urine collected. Young restressed the importance of this technique. The present-day use of the Papanicolaou smear technique is significant when positive, but a negative result certainly fails to exclude the diagnosis of bladder cancer. From the financial and technical aspects it is impractical at this time to use this procedure as a screening test. In our patients we have discontinued entirely use of this technique for the following reason: If the Papanicolaou smear is positive, cystoscopy is certainly indicated; if there were sufficient signs or symptoms of bladder tumor to warrant collecting urine and performing a Papanicolaou smear and it proved negative, cystoscopy is still indicated.

Treatment of Infiltrative Vesical Cancer

Once the depth of infiltration of the bladder cancer has been established by transurethral biopsy, what type therapy should be employed: radiation, segmental resection, cystectomy, transurethral resection with or without insertion of radon seeds, or some combination of these procedures? Unlike Don Quixote who went around tilting at windmills, urologists are practical specialists requiring a definitive plan of attack to this problem. The greatest percentage of cases seen by the urologists already have far-advanced, so-called "inoperable," cancer that has spread beyond the bladder and extensively involves the lymphatics, or metastases are known to be present. Statistically speaking these patients are managed best by palliative measures to control bleeding, urinary signs and symptoms, or uremia. This treatment consists of transurethral resection of the tumor with or without uretero-intestinal or ureterocutaneous anastomosis. Most urologists are in agreement with this program. Due to production of distressing vesical symptoms, few American urologists use only radiation therapy for patients comprising this group. One school of urologic thought contends that palliation in these patients is a defeatist attitude, and is in the process of exploring extremely radical pelvic surgery to determine whether or not it has any merit. As the results are not yet fully complete it is unwise to present definitive comment at this time. These surgeons are accumulating valuable data which will inevitably increase our knowledge of management of this disease.

Treatment of Non-Infiltrative Vesical Cancer

Only a small percentage of patients with vesical malignancy are seen by the urologist while the cancer is still confined to the mucosa, submucosa or superficial muscle layers of the bladder. None the less, this small group of patients have provoked the greatest controversy among urologists specializing in this field. It would appear advisable to discuss the rationale for surgery in cancer: As yet we have no cure for cancer other than radical surgery and, in some cases, radiation therapy. Curative surgery for cancer is based on the principle that at a particular time in its growth the cancer has not spread beyond the reach of the scalpel. The goal is to operate before the spread, while the tumor is still localized. Concerning bladder cancer this logically implies cystectomy. Most urologists contend, however, that the adverse effects of diversion of the urinary stream after cystectomy are fraught with so many complications that transurethral resection or segmental resection of the tumor are procedures of choice. In addition, it is contended, cystectomy fails to cure any more patients with cancer than these "conservative" procedures. This misconception has been based on statistics in which cystectomy was used generally as a desperate, heroic or "last ditch" procedure for far-advanced bladder cancer. In the majority of these reports cystectomy was resorted to only after more conservative treatment had failed; as such, they must also be classified as failures for conservative management and this is seldom specified. In addition, only a few of these reports stated whether or not any lymphadenectomy was performed in combination with cystectomy. It is understandable that these statistics offer such a poor rate of cure. Only a few reports have been published of cystectomy utilized exclusively for early or non-invasive bladder cancer. As may be expected, the results in the latter group are considerably more encouraging. While the complications of diversion of the urinary stream are real, pro tem consider the subject from the standpoint of good and bad cancer surgery. A thoracic surgeon would be subject to criticism if he encountered a carcinoma of the lung and removed only the cancer with a small cuff of normal tissue surrounding it and failed to remove the rest of the lobe of the lung. A general surgeon would be quite remiss, if operating on carcinoma of the lower recto-sigmoid he simply excised the malignancy with a cuff of normal tissue and closed the hole in the bowel wall. There are countless

similar examples pertaining to any surgical discipline treating cancer. The same urologist that rightly insists upon nephro-ureterectomy for a small cancer of the renal pelvis will perform local excision of a bladder cancer surrounded by a centimeter or two of normal bladder wall and then close the defect in the bladder wall. Another urologist will treat the same non-infiltrative bladder cancer by transurethral resection. The surgeon resects only that portion of the bladder that endoscopically appears to be involved with the tumor. Obviously, this norm is too subjective and entirely inadequate in many instances as we have demonstrated by deliberately performing total cystectomy a week or two following what appeared to be complete transurethral resection of the tumor. Second, the operator is restricted in his resection by fear of perforation of the bladder. Third, no lymphadenectomy is performed to remove the positive tumor bearing lymph nodes that occur in some 2 to 5 per cent of these cases. It would appear that generous segmental resection and lymphadenectomy or total cystectomy and lymphadenectomy obviate these objections and offer to date the best opportunities for cure in treatment of non-infiltrating bladder cancer. The fact that many non-infiltrating vesical neoplasms are cured after transurethral resection as now performed should not satisfy or placate the urologist. We are interested in improving our present statistics.

Hemicystectomy versus Segmental Resection: Based on recent human and dog experiments,[2] the author prefers to perform hemicystectomy in place of the previously used segmental resection in which the tumor and only a cuff of normal bladder were excised. In practice, hemicystectomy often involves sacrificing 1/3 to 2/3 of the organ with reimplantation of a ureter into the bladder. Prior to reconstruction of the bladder, lymphadenectomy is performed. Where the tumor is within 2 to 4 centimeters of the bladder neck, more radical surgery is employed (cystectomy). In addition, hemicystectomy is reserved for those patients in whom the tumor had been proven by biopsy to invade only the superficial layers of the muscle or less.

While it is true that hemicystectomy is probably unnecessary for very small bladder cancers, it is impossible to determine this fact selectively preoperatively at present without studying a larger series of patients treated by this method (sixteen at this writing). Experimental and clinical data obtained to date indicate that many of these non-

infiltrative cancers have spread a great distance within the bladder wall away from the small lesion grossly visible within the bladder. Regardless of whether hemicystectomy or segmental resection is performed, it probably should be in conjunction with lymphadenectomy.

Cystectomy: Cystectomy should not be reserved for the far-advanced cancer but rather for the tumor proven by biopsy not to have spread through the entire bladder wall. The use of cystectomy for infiltrative cancer is a surgical attempt to cure the surgically incurable in the opinion of the author. Previously we performed this operation for far-advanced cases with the same poor results reported by others. Later we utilized cystectomy for *all* early non-infiltrative vesical cancers. During the past several years it has been our opinion that cystectomy may not be necessary to effect cure of bladder cancers that are not within two to four centimeters of the bladder neck. Cystectomy requires about one hour of operating time, but the lymphadenectomy takes three to four hours. It should be stressed that lymphadenectomy is not to be construed as simple removal of lymph nodes, but clean, complete stripping of all tissues off of the internal, external, and common iliac arteries and veins, and also the lower aorta and vena cava.

Radiation Therapy for Non-Infiltrative Vesical Cancer: Radiation therapy has a definite though incompletely defined place in treatment of bladder cancer. Certain factors have been established and should be discussed. All radiation therapy is based on tumor dose. This dose may be delivered by external radiation or internal radiation by radium bomb, radon seed, radioactive silver wire or radioactive isotopes. As with excision of non-infiltrating cancers, the results of radiation therapy depend also on depth of infiltration of the cancer within the bladder wall. Statistics (particularly those from England and Sweden) compare favorably with those obtained by surgical methods of therapy for non-infiltrating vesical tumors. While radiation has the distinct advantage of sparing the patient surgery and its concomitant risks, it has associated disadvantages. Radiation of the bladder produces severe vesical spasm and irritability. Not infrequently ureteral strictures and hydronephrosis develop. Radiation therapy may or may not kill a localized vesical cancer (it is impossible to determine without subsequent surgical biopsy of the lesion), but it does not treat lymphatic spread. Perhaps treatment of non-infiltrative bladder cancers may be managed best by preoperative tumor radiation followed in two or three months by lymphadenectomy.

In management of a similarly acting tumor, Taussig and later Meigs, have obtained excellent results in treatment of early cervical cancers by this attack. As all bladder cancers are generally quite resistant to radiation therapy, a combination of radiation and surgery or surgery alone should probably effect the greatest cure rate.

Complications After Diversion of the Ureters

With more than sixty techniques for uretero-intestinal anastomosis already described in the literature, it would appear that the cause of the frequent unsatisfactory results may not depend per se on the method used but on other more fundamental factors. It has long been considered that stricture formation secondary to the normal healing process at the site of the anastomosis has been responsible for the hydroureter, hydronephrosis, pyelonephritis and uremia so often observed. A method to minimize this inherent defect by direct mucosal anastomosis has been proposed by Nesbit and others. It was the objective of a previously reported investigation from this laboratory[3] to point out that periureteral fibrosis and the resulting stricture was not the sole contributor to this distressing problem. Ureterorenal reflux of fecal-contaminated urine and impairment of conduction of peristalsis following ureteral implantation appeared to warrant consideration. Data obtained from these three studies will be discussed.

Ureterorenal Reflux: Reflux may occur when two conditions obtain: First, a patent ureteral stoma must be present; and second, intracolonic pressure must exceed intraureteral pressure. In the patients studied it was shown that after *ureterosigmoid* anastomosis the pressure within the colon exceeds that within the ureter before the defecation reflex is initiated thereby producing reflux. From our observations should the patient experience the desire to "void" he probably already has ureterorenal reflux of fecal-contaminated urine. The value of frequent "voidings" is obvious. Rectograms demonstrating this phenomenon were of resting pressures which does not take under consideration the known fact that intracolonic pressure is elevated 100 per cent during evacuation. Were this latter aspect investigated it would unquestionably reveal reflux of a greater degree than the 8 to 15 per cent incidence in our series and that of others.

An additional factor must necessarily be considered. Following any of the accepted techniques of uretero-intestinal implantation a certain

percentage of patients will have normal upper urinary tracts. Graves has noted that most patients comprising this category have nonmalignant disease. Our experience has been nearly identical, but may be extended to include all patients having normal ureters on preoperative pyelograms. It was interesting to observe that preoperative pyelograms were normal in all patients having normal postoperative films regardless of diagnosis. In these patients the crux of the explanation may depend largely on the preoperative physiological status of the ureter. This concept is not new. Draper and Braasch in 1913[4] cut the ureterovesical valve in normal dogs and found that reflux did not occur in most instances. They concluded that the check-valve action of the intravesical ureter is of contributory rather than paramount importance. In the absence of the valve, reflux may be prevented by the normal physiologic function of the ureter which compensates for the loss. This impression has been confirmed by our clinical data. In our hands the best results have been obtained by uretero-intestinal anastomosis if preoperative pyelograms revealed ureters of normal caliber, and by ureterocutaneous anastomosis if the x-rays demonstrated ureteral dilatation. Two explanations of this are possible: First, unless a deliberate narrowing of the ureteral stoma is produced (which then acts as a stricture), due to its greater circumference the dilated ureter anastomosed to the bowel is usually more subject to ureterorenal reflux than the normal calibered ureter; second, ureteral dilatation indicates increased retrograde pressure and frequently associated renal tubular disease. In patients with renal tubular damage minor degrees of acidosis may assume alarming proportions. Ureterocutaneous anastomosis precludes the possibility of hyperchloremic acidosis from urinary rectal dialysis observed in some patients with uretero-intestinal anastomosis.

Where uretero-intestinal anastomosis is employed, it has been determined previously[5] in humans and dogs that implantation of the ureters into the mid-descending colon creates a large rectosigmoid reservoir for urine below the stomata and reduces considerably the incidence of reflux. The level of urine within the rectosigmoid does not reach the height of the ureteral stomata prior to initiation of the defecating reflex unless the patient is recumbent. This important advantage is not an unmixed blessing, however, as it produces a slightly higher incidence of acidosis unless the patient is advised carefully relative to the necessity of frequent "voidings."

Ureteral Action Potentials: It is conceivable that the extremely high incidence of ureteral dilatation subsequent to uretero-intestinal anastomosis might be related to impairment of conduction of peristaltic action potentials following division and implantation of the ureter. In a report from this laboratory,[6] a study has been presented of an experimental investigation of ureteral action potentials in the normal dog. These results were then compared with electro-ureterograms obtained after re-anastomosis of the divided ureter to bladder, uretero-intestinal implantation and incomplete and complete occlusion of the ureter. In brief, the findings of this project demonstrated that the normal electro-ureterogram is usually triphasic in form. An occasional normal variant may be diphasic. Normal peristalsis is rarely associated with after-potentials. Transection of the ureter below the electrode does not significantly alter the normal electroureterogram. Re-anastomosis of the transected ureter to the bladder or implantation in the bowel also failed to produce significant abnormalities of peristaltic action potentials unless ureteral dilatation developed as a result of stricture. In control experiments these abnormalities were demonstrated also in the dilated, but intact, ureter, indicating these changes to be associated with ureteral dilatation and unrelated to impairment of propagation of conduction in a previously transected ureter. To a limited degree this study has been followed also in humans with identical results. It may be stated with some measure of confidence, therefore, that ureteral dilatation subsequent to uretero-intestinal anastomosis is in no way related to impairment of conduction of peristaltic action potentials.

Uretero-Intestinal Stricture: Probably the most important contribution in this connection was the investigation of Hinman and Weyrauch in 1942.[7] Their study consisted of uretero-intestinal and ureterovesical implantation in dogs. It was observed that healing at the stomal site occurred either by primary union and early epithelialization (re-anastomosis of ureter to bladder), or by granulation and cicatrization and late epithelialization (uretero-intestinal implantation). The latter condition obtained in the presence of infection and the dogs developed stricture, hydroureter, hydronephrosis and pyelonephritis.

This experimental demonstration of periureteral concentric fibrosis and stricture at the area where ureter traverses bowel wall has great clinical significance as a large percentage of patients with uretero-intestinal anastomosis have ureteral dilatation and hydronephrosis.

Ragan and his associates, Spain and Molomut and others demonstrated that by systemic use of cortisone, connective tissue formation could be inhibited in experimentally produced wounds. Integration of these concepts resulted in experiments reported previously from this laboratory in which it may be concluded that parenteral administration of cortisone does not reduce the normal amount of fibrous tissue in an *uninfected* healing wound uniting ureter to bowel. Infection at or around the site of anastomosis, however, acts as a stimulus for increased local deposition of fibrous tissue with resultant stricture formation. Apparently cortisone modifies or reduces this fibroplasia or stimulus-producing fibroplasia in the infected healing wound. This observation was confirmed by additional data published on the prevention and treatment of other ureteral and urethral strictures of the urological tract.[8] It is believed that this beneficial effect of scar tissue inhibition in the healing wound by use of cortisone is observed only in the presence of infection. It would appear to be of importance, therefore, to reduce to a minimum, bowel infection during the reparative stage by administering intestinal antibiotic drugs until complete healing of ureter to bowel has been effected. It has been determined previously that although cortisone retards fibroplasia in wounds, a firm union is effected in a maximum of three weeks. Cortisone and intestinal antibiotics may probably be safely discontinued at that time without subsequently developing a ureterointestinal stricture. Recent unreported observations indicate that the use of cortisone is probably of little value if sterilization of the bowel is maintained for three weeks postoperatively.

Acidosis and Pyelonephritis: The development of hyperchloremic acidosis remains as one of the principle complications after uretero-intestinal anastomosis. The responsible factor is dialysis of urinary chloride across the rectal mucosa before the defecation reflex is initiated. As this complication cannot be eliminated completely with this form of diversion of the ureters, these patients require indefinite follow-up in the office or out-patient department. Periodically, serum chloride and carbon dioxide combining power must be determined. This condition should be suspected if the patient develops weakness, leg pains or anorexia, or fatigues easily. Acidosis, if present, is usually easily controlled with oral administration of sodium lactate or bicarbonate and urging the patient to "void" more frequently. Acidosis is usually greatly exaggerated in the presence of hydronephrosis. There is still some con-

troversy as to whether acidosis can ever develop in the absence of renal disease. It is the opinion of the author that patients with moderately to markedly dilated ureters should have ureterocutaneous rather than uretero-intestinal anastomosis to nearly eliminate this complication. Ureterocutaneous anastomoses tend to develop ureteral retraction or strictures which must be dilated periodically.

Subsequent to diversion of the ureters (to skin or intestine), there may be occasional bouts of pyelonephritis. Most of these are adequately controlled with Gantrisin, but persistence of temperature or chills, backache, rectal tenesmus or even incontinence, indicates the need of a different antibiotic agent. Treatment should be vigorous and continued for at least one week after complete subsidence of signs and symptoms. Defunctioning the lower bowel of feces by a preliminary and permanent colostomy, after the method of Vest and Boyce, has a pronounced effect in preventing these infections.

Discussion and Conclusions

In aniline dye workers, clinical and laboratory investigations have demonstrated at least one etiological factor in development of bladder cancer. It has been shown that depth of infiltration of the cancer in the bladder wall is highly significant with regard to both therapy and prognosis. Potentially, non-infiltrative cancers that are treated by accepted, present-day techniques should result in about an 85 per cent cure. Infiltrative tumors treated by any or all methods should have a cure rate of about 15 per cent or less. It would appear from investigations in humans and dogs that if ureteral diversion is to be employed, patients will obtain the best results if dilated ureters are transplanted to the skin and non-dilated ureters are implanted in the bowel. Treatment of infiltrative bladder cancer is directed at palliation by transurethral resection, and in selected cases, diversion of the urinary stream. Statistics to date have demonstrated that cystectomy is usually not curative in these patients. In treatment of non-infiltrative bladder tumors the objections to transurethral resection have been indicated. Cystectomy or generous segmental bladder resection appear to be more reasonable therapeutic procedures.

Studies of vesical lymphatics in dogs and spread of non-invasive bladder tumors in humans have indicated that conventional segmental resection may not be satisfactory treatment. Hemicystectomy in con-

junction with lymphadenectomy appears more reasonable from data now available. What is visually only a small bladder tumor may have spread microscopically throughout one-third of the bladder wall. About 2 to 5 per cent of non-infiltrative cancers have lymphatic spread. Cystectomy or hemicystectomy without lymphadenectomy appears to be an inadequate procedure.

Whether or not the lower colon should be defunctionalized by permanent colostomy after uretero-intestinal anastomosis is still under laboratory and clinical investigation. Transection and implantation of the ureters to skin or bowel do not produce alteration of peristaltic action potentials. Experiments in dogs demonstrated that ureteral dilatation following uretero-intestinal anastomosis is usually the result of periureteral concentric fibrosis where the ureter heals to the bowel wall with the production of a stricture. This may be reduced to a large degree after ureteral implantation by the postoperative administration of intestinal antibiotic drugs to hold the flora of the bowel at a minimum until the ureter has healed completely to the bowel. Experimental investigation has indicated that about 8 to 15 per cent of patients with ureteral dilatation after transplantation have ureterorenal reflux of fecal-contaminated urine. This may be reduced by anastomosing the ureters to a slightly higher level in the bowel and having the patients "void" more frequently. The problem of hyperchloremic acidosis following uretero-intestinal anastomosis has been studied in humans and dogs and the conclusion is that it is due to selective reabsorption of chloride within the rectum prior to "voiding" and is aggravated in the presence of renal tubular damage. Adequate rectal evacuation and administration of alkali when indicated control this complication. Pyelonephritis may develop after ureteral diversion to skin or bowel and regular follow-up visits must be made by these patients.

Previously, most patients developed severe renal disease after uretero-intestinal or ureterocutaneous anastomosis. Clinical and laboratory investigations have contributed toward reducing these complications to a degree where it is observed in only a small percentage of patients so treated. It is reasonable to expect that further research will solve this aspect of the problem. In the meanwhile, additional controlled data are being collected and reported concerning more specific indications for the various therapeutic methods available for treatment of cancer of the bladder.

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CURRENT CONCEPTS IN THE MANAGEMENT OF FUNCTIONAL GASTROINTESTINAL DISORDERS

*Transcription of a Panel Meeting on Therapeutics**

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MODERATOR LAMRENCE S. KUBIE: I am sorry to have kept you waiting this evening, particularly those who have come out in such a wretched storm as this. One of the members of the Panel, Dr. Koelle, has not arrived even yet because of a delay in his train connections. I am sure he will be here within a few minutes. We tried to wait for his arrival.

Without further loss of time, because we are late, I will remind you that our speakers are: Dr. Thomas P. Almy, Associate Professor of Neoplastic Diseases, Cornell University; Dr. Robert B. Hiatt, Instructor in Surgery at the College of Physicians and Surgeons; Dr. George B. Koelle, Professor of Pharmacology at the Graduate School of Medicine, University of Pennsylvania; and Dr. Sydney G. Margolin, Associate Attending Psychiatrist at Mount Sinai Hospital.

Our problem, as you know, is the management of functional gastrointestinal disorders. Dr. Almy is going to open the discussion.

DR. THOMAS P. ALMY: My first task is to define what we mean by functional gastrointestinal disorders. I dislike this assignment; but it is necessary to clarify it first. I would suggest that by functional gastrointestinal disorders we mean those disorders of the intestinal tract which arise as part of the bodily accompaniment in reactions to stress, bodily accompaniments of emotion; and that these are, in effect, normal responses of man; that they occur in all of us to some degree, but that when prolonged or of excessive severity, they may produce such disturbances of average intestinal function as to lead the patient to his physician.

We should also include in this concept that which is a probability, but not a definite certainty, i.e., that when some of these disturbances are prolonged for a sufficient period or are of even greater intensity, they may result in organic damage to the gastrointestinal tract.

Next I will present to you an outline which I believe to be oversimplified, but which may serve as a basis for further discussion. We think of each of these units as having in common a basic physiologic mechanism, which is related to one of several common clinical entities.

Thinking first of the esophagus, we would think of the phenomena of esophageal spasm and of cardiospasm as functional disturbances of the esophagus, each related to disturbances in the act of swallowing, that is, related to its truly esophageal component, which, as you know, is a well organized peristaltic wave. The only difference between esophageal spasm, as I see it, and cardiospasm is in the state of tone of esophageal

muscle. In each there is incoordinate contraction of the esophagus. It would seem to exclude stimuli from the upper half of the gastrointestinal tract. This is brought into play by appropriately poisonous material, i.e., extremely hot or cold material, applied inappropriately in certain emotionally charged situations.

Second, we think of gastric mechanisms, which we commonly characterize as dyspepsia, as biliousness, and we find many symptoms associated with these syndromes: e.g., nausea, epigastric fullness, belching, and the like. The best studied symptom of this group is nausea. Here, as you know, the stomach is hypo-active. There is reduced motility and excretion of the stomach. Again, the biological significance of this probably is to exclude a noxious stimulus from the organism.

Third, and perhaps peculiarly placed in this outline, would be a type of disturbance of the small intestine. This is the most dubious member of this group. We might call it "non-tropical sprue." It represents, of course, a reduction in the motility and in the absorptive capacity of the small intestine; and it, too, may play a role in excluding noxious substances from the body. I would not be too sanguine about that; and I would not feel too badly if this mechanism were thrown out completely.

There is another mechanism to consider here, an opposite mechanism in the stomach, which is commonly associated with peptic ulcer, with gastritis or duodenitis. It is, of course, the mechanism of gastric hyperfunction, a well studied disturbance in gastrointestinal physiology, which has been associated clinically with moods of hostility and resentment, and which probably represents an important biological process in the organism: e.g., the preparation of the stomach to receive food. In lower animals this appears to be associated with the hunt; and one might say this is part of the psychophysiology of the hunter. It also is part of the psychophysiology of the crying baby, who has a vigorously contracting stomach. Thus it is part of the phenomenon of dependency upon another person for alimentation.

Then, there are two mechanisms of importance with respect to the colon. There is the mechanism that is commonly defined in clinical terms, and which physiologically probably represents a sigmoid spasm with relative hypofunction beyond the proximal portion of the colon. It would seem that we have here a mechanism which will prevent stool from entering the rectum, prevent the distraction of the animal or of

the man by the necessity of having a bowel movement during emergency situations. I shall not attempt to outline that on the blackboard.

Finally we have one other colonic mechanism which is definitely worth listing, i.e., the diarrhea of mucous colitis, and the questionable relationship of this to the disease we call ulcerative colitis. In this condition there is an exaggerated peristaltic wave in the colon, exaggeration of mass peristalsis. Biologically there is an effort on the part of the organism to rid itself of a noxious stimulus which has already been ingested.

The frequency of these varies greatly. Esophageal spasm as distinct from cardiospasm and non-tropical sprue are exceedingly rare phenomena clinically. Cardiospasm of the true type and ulcerative colitis are moderately common phenomena. Of course, dyspepsia, peptic ulcer, functional constipation and diarrhea are among the most frequent problems to be found in any physician's office.

MODERATOR KUBIE: Thank you, Dr. Almy.

The next speaker on our program was to have been Dr. Koelle. Since he has been delayed, I will call on Dr. Hiatt.

DR. ROBERT B. HIATT: There are two aspects to the role of the surgeon in treating patients with functional gastrointestinal disorders. The first role is the traditional use of his technical training in surgery to alleviate disease or to improve the patient's ability to cope with his illness.

Under that, there are several factors that ought to be brought out. First, I should like to point out that the assistance and interest of other physicians on the case should not cease when the surgeon operates. The surgeon by the fact of his performing an operation does not, therefore, exclude the role of other therapists. Conversely, the responsibility of the surgeon does not end with the operation.

As an example of this, I should like to mention the postoperative care of patients with ulcerative colitis. Surgery, through the alleviation of pain and acute discomfort, often prepares patients for the therapist. The operation alone does not cure the patient in toto. I will elaborate further on this later.

There are three functional gastrointestinal disorders that have been listed here that can frequently be helped by surgery. First, I would like to mention peptic ulcer. It is the general opinion among surgeons that partial gastrectomy is one of the best things we do for patients with this lesion. It is a pleasure to see a patient who is pain-ridden, economical-

ly handicapped and emotionally incapable of coping with any problem, change in a comparatively short period of time to someone who is economically and socially quite functional, by the use of surgery, and specifically by partial gastrectomy.

Of course, partial gastrectomy is not really indicated in duodenal ulcer until it has been proven that the patient is medically refractive. In 85 per cent of these patients, surgery is the only therapy needed, in the sense that subsequently they can function well, economically and socially. In the other 15 per cent, some additional form of therapy is needed. You can include in this 15 per cent group the group that get recurrent ulcers in spite of partial gastrectomy.

I cannot leave this subject without mentioning the association of carcinoma with *gastric* ulcer. This has been estimated to be 20 per cent of the total. This precludes long term medical therapy for this condition. We can all agree that we should no longer procrastinate with the gastric ulcer, even though the x-ray picture may be quite benign.

The second condition that I would like to discuss is cardiospasm. It is of interest to me that we include cardiospasm in the functional group, despite the fact that it has been demonstrated fairly conclusively that there is an intrinsic neurogenic defect in the esophagus. In severe cases, this can be proven histologically. Nevertheless, I think it is appropriate to include cardiospasm in the functional group; because the vast majority of patients with cardiospasm function well except when their anxiety load is increased. In other words, they respond to either dilatation or medical therapy except in moments of stress.

The third condition that I would like to discuss briefly is ulcerative colitis. There the indications for surgery are fairly definite. There are three of them. The first is where a patient would die without the operation. These are, of course, in the extremely acute cases. The second is where the disease is stabilized to a degree incompatible with useful life. This is the most common reason for colectomy. The third reason is where there is a threat of malignant change. This refers to the long standing cases, particularly those whose illness began in a quiescent area and smoldered intermittently for years. The incidence of carcinoma in that group is extremely high.

I would like to discuss briefly the second general aspect of the role of the surgeon: namely, as a physician in general. First, under that category, is his aiding in diagnosis, which includes biopsy or examination and con-

sultation with other therapists. The second is the treatment of those patients who are referred for surgery, but who do not necessarily have a surgical condition. Under this category, it is important for the surgeon to have an awareness of psychological factors. As an example of this, I will mention a case of spastic colitis. A patient I saw recently had had an accident approximately fifteen years before, in which he had sustained a severance of his external rectal sphincter. An acute infection followed which further destroyed some of his sphincter mechanism. This finally held, and he was functional. He was able to control his bowels for these fifteen years until approximately six months before seeing me. When he came into my office he was convinced that he needed an anoplasty to repair it.

On examination, he had quite an impressive defect of his anus, and it would have been quite easy to assume that this patient could perfectly well be cured by surgery. However, on looking into the situation more carefully, it became obvious that through a distressful situation involving an emotional relationship with his wife, this patient had developed, on top of his anatomic defect, a spastic colitis; and it was comparatively easy to discuss the entire problem with him, and to point out that in spite of his defect he could carry on perfectly well if we could reduce the amount of emotional energy that was being expressed via his colon.

This sort of situation is common in surgical practice; and the surgeon is often placed in the position of having the confidence of the patient to a point where it is up to the surgeon to help the patient to seek other forms of therapy, where that is indicated.

We have not included pruritus ani in this group. I would like to use that as an example of a situation where the surgeon frequently is the only one who can guide the patient into proper hands, or who can actually treat the patient, because of the particular gratification that patients often get from having some form of frankly, "laying-on-of-the-hands" by the surgeon. Pruritus ani is, in my estimation, simply a neurodermatitis of the anus. It can be a very disabling condition. With understanding of the emotional background, one can cure all of these patients. if they are seen within a year of the onset of the illness. I have been particularly struck by the fact that once the disease has assumed a deeply ingrained pattern, it is almost impossible to cure pruritus ani. This is the situation where the surgeon can intercede, and in a more or less non-surgical manner induce patients to seek proper care.

Also, the surgeon must be able to understand postoperative patients. In other words, the anxiety factors in postoperative patients can ruin surgical results; and the surgeon must have some awareness of emotional factors if he is to get patients through an operation as smoothly as possible.

MODERATOR KUBIE: Thank you, Dr. Hiatt.

We are still running behind schedule because of our delay in starting, as we waited for our storm-bound panelist, Dr. Koelle. Therefore without comment, I will call on Dr. Margolin.

DR. SYDNEY G. MARGOLIN: My point of view is that of a psychiatrist, with some familiarity with the somatic conditions described by Dr. Almy and Dr. Hiatt. I will not take up the individual diseases or syndromes that are mentioned, except as they appear in the later discussion.

In general, I would like to discuss two aspects: one having to do with diagnosis, and the other with treatment. From the point of view of diagnosis, there are various theories which hold that individuals with one or the other of the diseases described by Dr. Almy have particular "personality structures," or "personality profiles" or that they develop these diseases in the presence of certain specific kinds of *conflicts* in the world in which they live, or in their relationships with special members of the family, or with society. These theories of the specificity of the profile, or the specificity of the conflict are under heavy fire from a variety of people who have attempted to test them, both clinically and statistically. If the discussion should warrant it, I will be glad to go into details about them.

For the moment it suffices to say that all of these diseases represent many psychological factors, either contributing to the etiology of the disease (never the sole etiology, but one of the important factors), or the psychological factor may occur as a consequence of having the disease; and, finally, it may occur in the process of recovery from the disease. Each of these phases requires diagnosis and management in order effectively to help the patient.

There is one condition which has not been mentioned by Dr. Almy, because it is not a condition to which an internist or a surgeon can attach a diagnosis. This is the condition in which the patient complains of symptoms which cannot be identified by any method of physical or physiological examination. These are usually classified under the general psychiatric diagnosis of hypochondriasis. There is a form of malignant

hypochondriasis in which the symptoms are expressed in the form of a delusion, and where there is no somatic basis whatsoever for the symptom. Or the patient may pick out some old or obsolete symptom of some past illness in a part of his body, and use this to express a circumscribed psychological illness.

It is important also to know that these are illnesses which frequently may mask an underlying depression, a psychosis or paranoia; and that often some of these illnesses, particularly some forms of ulcerative colitis, may actually alternate with a psychosis or a neurosis.

From the point of view of treatment, I would like to read a summary of some current opinions on therapy from the psychological point of view. It should be stressed that psychotherapy is an adjunct to all of the therapies that are recommended by Drs. Almy and Hiatt and, of course, to the drugs which I think Dr. Koelle will discuss when he arrives.

Most clinics which apply the psychosomatic point of view (that is, the point of view of comprehensive diagnosis and comprehensive treatment of a patient), arrive empirically at the realization that so-called superficial psychotherapy is the management of choice. Such psychotherapy consists in a common sense approach by means of tolerance, indulgence, allaying of anxiety by all available trial and error means, by demonstrating friendliness and reassurance, by deliberately omnipotent behavior on the part of the doctor, for the purpose of enhancing confidence in him, plus total somatic care in terms of nutrition, medication and hygiene in an agreeable environment.

All of the personnel of the home, clinic, or hospital environment can participate in this program, under the supervision of the doctor. There may also be a good deal of manipulation of the environmental circumstances of the patient; the sort of thing that we are accustomed to arrange through the social workers in our hospitals.

In short, superficial psychotherapy is an aspect of a patient's treatment which can be recognized as one of the supreme forms of the art of medicine.

What I have said is nothing new to all of us here as physicians. We do this sort of thing spontaneously with some of our patients, if not all. For patients who are severely ill somatically, in the functional groups described by Dr. Almy, any uncovering psychotherapy, that is, prodding into the patient's unconscious in a hurried and perhaps an unmeasured way (aside from the practical disadvantages that the patient is too ill to

wait for the results of any prolonged psychological investigation), not infrequently makes the patient worse. It seems to exacerbate the morbid process. Those physicians who are successful in their management of patients with psychosomatic diseases, appear to possess the art of medicine in the highest degree. This is a trait in a physician, and not something that ordinarily can be communicated or taught. It is possible, however, to transmit some of this art in terms of the nature of the psychology of what goes on between a patient and physician, thus converting what has always been known as the art of medicine into the science of medicine. That is, it is a trait that may be taught to us as students and practitioners.

One of the striking features of remissions and relapses in this group of chronic and recurrent illnesses is the close association of a mood change with the remission or the relapse. If, for example, a patient with a peptic ulcer, or ulcerative colitis, or neurodermatitis of the anus, for any reason, not at all associated with the somatic process, goes into a depression, there is likely to be a relapse of the chronic disease; whereas, a remission of the organic syndrome is usually accelerated during elevated moods.

For this reason, therefore, the old-fashioned idea of urging some of our patients to take voyages or go to comfortable environments, when they can afford it, was not a bad idea, in the sense that any such self-indulgence makes many people feel good about themselves, particularly if they have the authority of a physician whom they respect to justify the self-indulgence.

This close correlation between depression and euphoria on the one hand, and relapse or remission on the other, does not apply to all functional disturbances. For example, the asthmatic symptoms of a dry spastic state are not frequently aborted or relieved by emotions associated with cheerfulness: more often they may be relieved by tears. To make a general statement, emotions, effects and moods so alter the pathophysiology of a given disease as either to increase or diminish its intensity.

In other words, the emotions act as though they were drugs. You can have emotions which act as if they had parasympathetic influences and others which seem to have sympathetic influences, and to that extent they can neutralize or enhance the effect of any given medication.

MODERATOR KUBIE: Thank you Dr. Margolin.

I was about to read Dr. Koelle's statement when I have received word

that he is near at hand, and will present his material himself. While waiting for him we can consider a few questions submitted.

First, could you, Dr. Almy, say something about "regional ileitis?"

DR. ALMY: There is much circumstantial evidence to suggest that the symptoms of regional ileitis coincide with emotional tension, i.e., with periods of stress in the patient's life. This coincidence has been the jumping off point for critical experimental study of this phenomenon in other diseases.

I do not believe that anyone has characterized the personality of such patients sufficiently to suggest that there is a specific relationship between the disease and any one type of personality. Nor has the mechanism by which the physiological disturbance as a bodily accompaniment of emotion been established in the etiology of this condition. Hence, I am inclined to reserve judgment on that question.

MODERATOR KUBIE: Thank you, Dr. Almy.

Dr. Hiatt, you have been asked whether you accept the general concept that emotions can produce severe disease of the gastrointestinal tract.

DR. HIATT: I can say categorically that I do accept that concept. I would like to elaborate on it.

We all make the mistake, (probably because it is difficult to speak about the dynamics of these illnesses) we all make the mistake of dividing our thoughts into water tight categories: emotional, physiological, and organic. It would be better to accept the fact that in somatic patients any emotion is both a psychological and a physiological event. One should not think of an emotion as something magical going on in the cortex of a patient. In ulcerative colitis, which has been my interest for a number of years, all emotional energy is funneled through the colon. We have already been able to document this physiologically. But added to this is a persistent inflammatory reaction which waxes and wanes, according to the amount of abnormal physiology.

I believe that the same is true of ileocolitis. We know that an emotion, with its physiological counterpart, makes the inflammatory process which makes an ulcer; and that this is a persistent phenomenon which causes degeneration of the gut.

MODERATOR KUBIE: *While you are on the spot, someone wants to know how you feel about the cure or relief of cardiospasm; whether it can be cured by medical means alone, or by dilatation of the esophagus, or by gastrostomy.*

DR. HIATT: In this condition the patient must cope with a real physical defect. He can cope with this physical defect only as long as his emotional energies are coordinated. When emotional stress passes his threshold, then the physical defect is activated by the emotional energies.

Since this is true of cardiospasm, dilatation and medical therapy are palliative, not curative. Dilatation alone may be adequate in the average case; but it would be effective far more often if it were regularly combined with some type of psychotherapy.

Surgery in cardiospasm should be reserved for those who can not maintain themselves by medical treatment, including dilatation. The surgical results in this condition are not good enough to warrant indiscriminate operation in cardiospasm. Some of the results are excellent. On the whole, however, they are somewhat disappointing; probably due to the fact that the abnormal physiological pattern of the esophagus persists.

MODERATOR KUBIE: Thank you.

Next come a group of related questions about the problems of ulcerative colitis and peptic ulcer. I will ask Drs. Margolin and Almy to consider them together. These questions center around these issues: What percentage of these cases arise predominantly on a psychogenetic basis as opposed to other factors? What percentage of remissions can one expect from psychotherapeutic maneuvers, either alone or predominantly? How do you select the cases in which to place a major emphasis on psychotherapy, and those in which you will place your major emphasis on drugs?

DR. MARGOLIN: I will start with the question of psychogenesis (i.e., psychological etiology). The word psychogenesis is in our language; and we appear to use it meaningfully. Yet probably, strictly speaking, there is no such thing. If used literally, the term implies that a psychological disturbance arises de novo in the mind, and then proceeds to manifest itself in the form of a psychophysiological influence. This is not accurate. The mind is only a link in a chain of circumstances, beginning with the perception of a stimulus, which is in a sense exterior to the mind, and then combining with the other properties of the mind to create or participate in a disturbance which we call an illness. Thus the term psychogenesis does not apply, if used in an exact sense.

If the term is used correctly to indicate that a disturbance arises as a reaction to a situation which does not impinge on the gastrointestinal

tract physically or tangibly, but which impinges upon the mind and then indirectly is associated with a disturbance in function, perhaps we can try to answer the question.

From this point of view, I would say that every disease, not only ulcerative colitis, but such things as malignancies, traumatic injuries, the course of disease, in some cases the etiology and in other cases the consequences of disease, are all influenced by the participation of emotional factors.

As to the effect of psychotherapy, I do not know of any case of ulcerative colitis that has been treated solely by psychotherapy. I know of cases in which, after the interruption of treatment, the patient entered into psychotherapy during a quiescent stage of the disease, or in a phase of fair equilibrium and under the control of medication. Most patients with ulcerative colitis, if they are receiving psychotherapy, are simultaneously receiving some form of medical management, and are being controlled by internists along with the psychiatrist.

The case in which psychotherapy plays a major role is the type of patient I am accustomed to see on our service at The Mount Sinai Hospital. Characteristically this patient is regarded as too ill for surgery, and despite the application of the best that the medical service has to offer appears not to be gaining ground; and in fact, may even be losing ground. Such a patient usually has been allowed to go too long; but this notwithstanding, such a patient would be considered for psychotherapy as well as for comprehensive medical management.

The reason why one selects patients of this kind in order to come to a conclusion about the effectiveness of psychotherapy is that this is a disease which is characterized by spontaneous remissions; and it is only if you intervene successfully with psychotherapy in a patient whose course is downhill, and who has been given up by other medical disciplines, that one may allow oneself to conclude with reasonable probability that your maneuver was the effective corrective agent. It is with such patients that our experiments in psychotherapy have been performed.

DR. ALMY: I would like to say something about what per cent of patients are cured by psychotherapy alone. I agree with Dr. Margolin that there are few patients with either condition who have been treated exclusively by psychotherapy.

A few years ago we tried to set up a controlled study of the effects of simple psychotherapy in duodenal ulcer. We treated 150 patients

without psychotherapy, providing those elements of diet, alkaline medication, and so on, which are commonly recommended. We treated 150 other patients with the same measures, *plus* approximately twelve hours of simple psychotherapy of the kind that one might expect any practitioner to provide.

At this time, about three years following the conclusion of the active phase of this study, we have essentially the same result in the two groups of cases. I do not know what this means, unless perhaps it indicates that the conscious elements in psychotherapy in the hands of the ordinary physician are not the important ones. Or perhaps we were unable to exclude psychotherapy from the control group.

I mention this partly to tell you directly of the results, partly to indicate that we lack an adequately controlled experiment with which to answer the question about the therapeutic effectiveness of psychotherapy in this situation.

MODERATOR KUBIE: *Dr. Margolin, is there anything you would like to add to that now?*

DR. MARGOLIN: No.

MODERATOR KUBIE: *With respect to the efficacy of psychotherapy at various levels, you alluded before to certain dangers. Dr. Almy has indicated, on the other hand, that there is at least the possibility that if we always play safe, we may make ourselves ineffectual. How can we resolve that dilemma?*

DR. MARGOLIN: The idea of danger is connected not with psychotherapy as a whole, but with a specific type of uncovering approach to the patient. That is, you confront the patient with insights into his own unconscious, with insights into his emotions, or into attitudes of which he had been unaware. One does not have to be somatically ill, to find such situations extremely distressing. In any argument, one of the best ways of demolishing your opponent is to point out something about his character or his makeup or his attitude, which he would rather not know. Under such circumstances all of us react with some visceral changes. Patients who are severely ill with ulcerative colitis, patients who are suffering from peptic ulcer or an inflamed colon, or other functional disorders, if confronted bluntly with the patho*psychology* of their patho*physiology* will inevitably become sicker. It is from this point of view that I speak of the dangers of brusquely confronting any such patient with the unknown layers of what is on his mind. It is from that

point of view that I regard it as dangerous.

In line with what Dr. Almy has said, I can endorse the psychological approach he has outlined most heartily, and would like to confirm the fact that whenever you give medication to a human being, although you may not say a word or make any recommendations about the medication, the act of prescribing may be regarded as an act of great sympathy, or even of great affection. Or a paranoid patient may regard it as an act of great hostility; as though you are trying to poison him. Excluding that possibility, however, most patients will regard any gesture, with or without words, or words without gestures, with or without medication, as of enormous value and support.

DR. ALMY: Is it not fair to suggest that this is perhaps the most efficient method of simple psychotherapy in the hands of the thoughtful physician?

DR. MARGOLIN: Yes.

MODERATOR KUBIE: I would like to put a spoke in the wheel. How does a physician persuade a patient with an organic disorder to accept the idea that he needs psychotherapy at all. In my private office, where a patient comes of his own accord, knowing that as a psychiatrist I approach this problem from a psychosomatic point of view, the patient has arrived already half convinced, or he would not come at all. I do not need to persuade him. Indeed, quite the reverse, I have to try to make him face his doubts; because often he is convinced only on the surface; and we know that under these circumstances he may go through the motions of accepting psychotherapy without actually facing up to his problem. He may be coming simply to accede to the wishes of his family, or to show that he is a good boy and willing to do anything to get well when, in reality, he far prefers his organic disorders to the pain of facing emotional problems.

But all of this contrasts sharply with the situation which confronts us when we deal with ward patients who are accustomed, by and large, to doing what they are told, and to accepting any specialist who is sent around to see them for a checkup or an examination. The patient's cooperation in going through the motions of accepting psychotherapy is something you can be almost certain of. But whether he really accepts this internally is another matter. And the problem is how to tell and how to persuade.

I would like to ask Dr. Hiatt to start this off, because he must face

this problem constantly when he deals with patients who are sent to him for surgery, only to become convinced that they need something in addition to the surgeon's scalpel. Dr. Hiatt, how do you, as a surgeon, who is also the antechamber to a combined multi-disciplinary approach, how do you approach this problem?

DR. HIATT: Frequently you face a patient with a psychosomatic condition, whom you want to send for skillful psychiatric care, and you are constantly being confronted with terrific hostility on the part of a patient to acceptance of that point of view or to psychiatrists in general. (Unfortunately, among lay people, there still is a stigma attached to being treated by psychiatrists.)

So, instead of hitting him over the head with my convictions, we start discussing a few problems that are non-traumatic to the patient, but where the patient can finally be led to see that there may be some relationship between certain problems and his disease. When necessary, I explain the neurophysiological pattern that links them. This impresses the patient. Then, at the end of a period of such discussion, I say: Do you realize that for the last fifteen minutes, or half an hour, you have been in a psychiatric interview? Is it so bad?

They have to be taught. You have to spend a great deal of time telling them that psychiatrists are not ogres and are not going to destroy them, and that it is to their benefit to go and that you will not abandon them, but will carry on along together with the treatment if they will accept this form of therapy.

If you find after a short period of time that you cannot get anywhere, then you might as well abandon the attempt and treat them as best you can medically.

MODERATOR KUBIE: Thank you.

What would either of the other panel members say on this point?

DR. MARGOLIN: One of the best ways of introducing a patient to the psychological management of his disease, is with something to eat. This is the best way of handling most people, or more correctly most children, since these patients have regressed in their social and emotional points of view about themselves and their environments to childhood.

The best way of appealing to any regressed person, adult or child, is with something to eat. One of the ways of doing that, for example, with a patient on a ward, or even a moribund patient, is to suggest that he eat something not included in the usual inflexible and rigid diets

offered to him. As you will see from the list of diseases described by Dr. Almy, restricted diets are important in the treatment of most patients.

A patient whom I recently saw will illustrate this. This was a woman who had lost a great deal of weight and was quite anemic. She had ulcerative colitis. She was toxic. She was on a low residue diet of the usual kind. Discussion with her brought out the fact that she had refused any kind of psychological management. During these initial discussions, however, she did not know that I was a psychiatrist. I encouraged her to order anything her heart desired and she asked for a bacon and tomato sandwich, with lots of mayonnaise, and some frozen cantaloupe. This caused the nurse beside me nearly to collapse; but I ordered it immediately, at my own expense, in the hospital. The patient consumed most of that. After that, she challenged me, and wanted dill pickles, frankfurters and some Italian salami. She got that, too. She thought very well of me. This was an extremely intelligent woman. She held a position of some responsibility until she became completely disabled by her disease.

In this way, one can make an intimate and far-reaching contact, even with a patient who is regressed because of severe illness of any kind, which will cause the patient to idealize you. That is a good basis for psychotherapy.

MODERATOR KUBIE: *I am going to take advantage of my role here to cut into the stream of our discussion at this point. I purposely withheld the problem of drug therapies, hoping that Dr. Koelle would arrive; and he has. To fill in this important gap in our discussion, I am going to ask Dr. Koelle to turn to that problem directly.*

DR. GEORGE B. KOELLE: I might say that the most direct way to bring on functional gastrointestinal attacks is to spend five and a half hours, driving from Philadelphia to New York in a snow storm.

We might start by pointing out that the motility and the secretory activities of the gastrointestinal tract are largely autonomous, controlled by the intrinsic nervous network and, apparently, by the muscle fibers and the secretory cells themselves. In spite of the control which the central nervous system and the autonomic nervous system exercise over both patterns, we can modify the motility and the secretion by the use of drugs which act at different levels.

It is important to remember that when we use drugs, regardless of the site of action, we are providing symptomatic relief; and if this symptomatic relief is properly integrated with a proper diagnostic workup,

and the proper use of psychotherapy and surgery which have already been discussed, drugs can be extremely valuable adjuncts.

All drugs have side effects, and oftentimes in order to secure the therapeutic effect we must accept the other actions. With this factor in mind, we might take up one specific condition and mention some of the drugs that can be used in its control, and the levels at which they act predominantly. In peptic ulcer, we know that regardless of the type of therapy used, the chief aim of the therapist is to reduce the gastric acid secretion; and secondly, motility.

We will consider the mechanism of acid secretion by the stomach regardless of etiological bases. This has been somewhat artificially divided into a digestive and an interdigestive phase. The digestive phase can be further broken down into three components: the cephalic phase, the gastric phase and the intestinal phase. The interdigestive phase is vagal. Furthermore, if vagal activity is diminished, acid secretion is decreased during all phases.

In considering examples of drugs which can do this at various levels we can start with the central nervous system itself. Here various sedatives can reduce vagal activity. Proceeding peripherally to the autonomic ganglia, one might cite the use of Banthine or Prantal to produce vagal ganglionic blockade. Going further to the periphery, atropine and other anticholinergic drugs block the actions of the vagus directly at the effector (secretory and smooth muscle) cells.

There are other types of drugs that can be used for this same purpose. As a recent example, the carbonic anhydrase inhibitor Diamox interferes with the secretory mechanism by which hydrochloric acid is produced, and has received therapeutic trials in peptic ulcer. Also certain local anesthetics, such as procaine, apparently can cut down on vagal activity and on the liberation of gastrin.

In addition certain drugs are used to counteract acid secretion, such as the antacids—aluminum hydroxide and magnesium trisilicate. Antipepsins and antilysozymes, such as alkyl sulfates, have also been employed.

In using any of the foreign drugs the important things to keep in mind are that they are ancillary therapies and that we must accept certain side effects. Furthermore, even though we can control the effects of peptic ulcer with the drug, the patient and the physician should not be lulled into a sense of false security, when the symptoms appear to be

adequately controlled for the time being.

MODERATOR KUBIE: Thank you, Dr. Koelle, very much.

Our time is running out. Indeed we are late already. *Yet I want to ask Dr. Koelle some questions which were submitted before he arrived and which should be discussed. With some of these questions others on the panel may also be concerned. What about the role of the newer drugs, like cortisone and ACTH in some of these conditions?*

DR. KOELLE: Some workers, notably Dr. Seymour Gray at Harvard, have reported excellent results with the use of ACTH and cortisone in the treatment of ulcerative colitis. They have pointed out that ACTH and cortisone are both excellent in the early stages. During an acute fulminating flare-up, by the proper use of either of these agents the inflammatory response can be minimized; and patients have been kept in a state of remission for as long as two or three years. However, they may also interfere with healing; and the possibility of developing fistulae must be kept in mind. At any sign that these are developing, therapy with these drugs should be discontinued.

MODERATOR KUBIE: *I am going to keep you on the spot a moment longer. Then from the various questions which have come up I will ask Dr. Almy for the answer to one final question.*

What about the question of drug therapy at the higher levels?

DR. KOELLE: That, I am afraid, is where we have a great pharmacological hiatus. We probably would be getting much closer to the seat of the problem if drugs with selective actions at such sites were available. The only thing I can suggest at the moment, is the use of barbiturates and other sedatives.

MODERATOR KUBIE: *It has been my experience that the barbiturates, rather than acting as a sedative, may actually release trouble. I wonder how the others on the panel feel about that? But I am afraid we are already overstaying our time. Dr. Almy, will you take the bull by the horns? Would you be willing to outline what you might call a general therapeutic program, which might satisfy all of the members of the panel in some manner?*

DR. ALMY: I am not sure it will satisfy all the members. Could we have the lantern slide, please?

This is referred to as the fire cracker diagram; and has been in use for some time to stimulate our thinking about the various steps in the management of a gastrointestinal disorder. You will see that the chain

begins with a small fire cracker in the vision of our individual here, and that this fire cracker is unlit.

This represents the effect of the individual's attitudes and states of feeling as these modify the nature of the actual environmental stimulus to which the individual is subjected. He reacts not to the actual stimulus, but to his conception of it, by an integrated bodily reaction which is here represented entirely in terms of the nervous system and the gut. Of course, it involves other organs at the same time. Thus it is probable that the integrated mechanism also involves the endocrine apparatus. Nevertheless, this is the representation of pathways which may involve the brain, the spinal cord, the nervous system and, finally, the intestine. This is shown up merely to represent the levels at which this dynamic process can be attacked.

First, one may remove the stimulus. One may throw the fire cracker away, or put it in a bucket of water: i.e., one may send the mother-in-law out of the household. Secondly, one may attempt to modify the individual's attitude toward his environment in general. This, one could suggest as the object of well-oriented psychotherapy of all kinds. Thirdly, one could attempt to interrupt this integrated response in its neural pathways at the various levels which Dr. Koelle has just suggested: in the central nervous system, in the ganglia, at the end organ. Finally, one may attempt to affect the function of the end organ itself either by agents acting on the muscle or the secretory cells, or by agents which neutralize the effect of these abnormal functions, agents such as antacids to combine with the excessive acidity, in ulcer, for example.

Finally comes that about which we are rather more familiar in the management of these disorders, the elimination of the ancillary stimuli to disturb the gastrointestinal tract: e.g., the cup of coffee, the Manhattan cocktail, the hot dog with mustard. These are customarily eliminated from the regimens of many of these patients; but I think that they have an auxiliary role to play in the management of such a disorder.

MODERATOR KUBIE: Thank you, Dr. Almy.

Before we break up, I would like to ask what the others want to add to that.

Dr. Margolin, before you slip away, I have a feeling that you may have one important point to make that otherwise might escape us. Precisely what is this therapy which you have at times described under the heading of anaclitic therapy, as a regimen in a hospital? We cannot take

time for a long discussion. Could you give us in a few words what its essential nature is, to supplement what Dr. Almy has said?

DR. MARGOLIN: Anaclitic is a word that is based upon a term derived from psychoanalysis. The essence of it is this: As I have said before, when a patient becomes physically ill, he becomes somewhat child-like in his dependence on environment. He is somewhat child-like in his frustrations. Regression is then a spontaneous reaction in the patient, and actually helps him to get well, because he accepts what a well-intentioned environment wishes to do for him.

If such a patient, however, has regressed still further, that is, if he is enabled to become still more of a child than he appears to be, this is associated with an agreeable state of mind, a kind of euphoria, which engenders a psychophysiology which opposes the pathophysiology of the disease process.

The way in which the patient is regressed is done along primitive lines, as with food, about which I made some remarks a few moments ago. From a psychological point of view, the physician or the therapist deals with the patient on a non-verbal level; that is, he says very little, except reassuring words. From the patient's behavior and his verbalizations he deduces what the patient really wants. This can be done with a fair degree of accuracy, because when we are sick most of us want the equivalent of T. L. C., tender and loving care, and all of the symbolic activities which go along with T. L. C. If we receive this for a week or ten days, we ourselves tend to soften, and the strongest of us like to be babied along. In anaclitic therapy we purposefully encourage a degree of regression which exceeds that which the patient ordinarily would develop spontaneously.

MODERATOR KUBIE: I want to thank all the members of the panel, and to thank all of you for your friendliness in coming out on such a wretched evening.

IN COMMEMORATION OF THE HUNDREDTH ANNIVERSARY
OF THE BIRTH OF

PAUL EHRLICH

1854-1954

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JEAN A. CURRAN ..... *Presiding Chairman*

Section on Historical and Cultural Medicine
The New York Academy of Medicine

GREETINGS AND REMARKS

HANS E. RIESSER

Consul General of the Federal Republic of Germany

THE ERA OF PAUL EHRLICH

OWSEI TEMKIN

Associate Professor of the History of Medicine
Institute of the History of Medicine
The Johns Hopkins University, Baltimore, Md.

PAUL EHRLICH—MAN AND SCIENTIST

ERNST JOKL

University of Kentucky
Lexington, Ky.

PAUL EHRLICH IN CONTEMPORARY SCIENCE

CORNELIUS P. RHOADS

Scientific Director, Memorial Center for Cancer and Allied Diseases
Director, Sloan-Kettering Institute for Cancer Research

INTRODUCTION

IAGO GALDSTON

Executive Secretary, Committee on Medical Information,
The New York Academy of Medicine

PAUL EHRLICH is the embodiment of all the knowledge and wisdom that enter into chemotherapy. The pinnacle of his fame is *salvarsan,* the arsenical which he created, and which was in effect the first great modern chemotherapeutic agent. But that pinnacle tops vast achievements founded upon broad knowledge and experience. Paul Ehrlich's was a catholic intelligence that illumined whatever it embraced. There is enough glory in his life's work to have assured fame to a score of men, and enough inspiration in his unfinished work to feed the imagination and to nourish the curiosities of several generations. We know him principally as a chemist, as the man who converted a chimerical dream into a lifesaving reality. We are prone to fancy him puttering among his chemicals, trying with devoted patience and unflagging faith, now this, now that combination, one, ten, a hundred different ones, till the *606th* yields him the alchemist's dream, the great elixir. But true as this fancy may be in detail, it is faulty in representation. The man cannot be seen either in the way of his work, or even in its fruits. He can be seen only in his thought, in the inspiration that guided it, in the light that made it luminous.

Ehrlich was more than a chemist. He was a biologist in the profoundest sense of that term. He had a long and thorough apprenticeship in the fundamental biological sciences, and to each he contributed precious new knowledge. He traveled the long road and all the bypaths that lead to chemotherapy, and toiled with every step. His crowning achievement was not a gift from the gods, a lightning stroke of genius, a fortunate inspiration. It was rather a precious nugget reduced in the crucible of long and hard toil, from the crude ores mined with heart-breaking effort. His Faustian spirit sought for knowledge in many spheres, in the respiration of cells, in the analyses of dyes, in the fine structures of the brain, among the bacteria, and the garden herbs. He quizzed nature on the mystery of immunity and wrested from her some portion of her secret. He dipped deeply into the problem of malignant growths and left upon it the imprint of his thought, so that to this day his theories are respected, and his hypotheses are the signposts of future research. He, who was trained as a physician, proved himself a master chemist, and as both chemist and physician, he gave to man the protean vision of chemotherapy.

GREETINGS AND REMARKS

HANS E. RIESSER

Consul General of the Federal Republic of Germany

IT IS a great honor and privilege for me to be invited tonight when you are celebrating the 100th anniversary of Paul Ehrlich's birthday. I must tell you quite frankly, though, that I was somewhat embarrassed when I received your kind invitation. Here I am speaking before a distinguished group of outstanding physicians and scientists who know more about Paul Ehrlich and his work than I do. I personally, a doctor of civil law only, do not feel qualified to address this assembly on the subject of a medical genius like Professor Ehrlich, but I am very proud that as a Representative of the Federal Republic of Germany I was asked to speak about this great German.

There is little I could tell you about his scientific achievements. You all know that Paul Ehrlich as physician, chemist and biologist devoted all his life to serum research work in the field of contagious diseases. My only personal experience with serum dates back to my early childhood when I had a serious attack of scarlet fever. Five doctors whom my father summoned, gave me up as hopeless. They asked permission to use a newly discovered serum. My father agreed, and I was inoculated with the serum which was made from the blood of a horse. The horse died the following day and I survived. I still remember that I wept when I heard about the poor horse—a white one it was. The case was widely discussed in medical publications and there was some question whether my recovery was due to the serum—or my having the constitution of a horse!

But to get back to Paul Ehrlich. Fortunately I am in a position to say something about his character, his personality, and his charm because members of my family knew him very well. I would like to mention my late brother Otto, a professor of pharmacology at Frankfurt University. And there is another relative of mine connected with Paul Ehrlich: my cousin Professor Ferdinand Blum, himself a great scientist, who was Paul Ehrlich's friend and doctor. Ferdinand Blum who now lives in Zuerich

and is almost ninety years old, is still hard at work. He has been asked to speak at the Frankfurt celebrations in honor of Ehrlich and von Behring. I wrote to him with a request for some details on Ehrlich's life. He replied immediately, and I am going to read you part of his delightful letter:

"Paul Ehrlich had a charming and truly sunny nature. He needed that sun, too. Tempests and upheavals in his life depressed him and disturbed the quiet which he required. Yet, he did not allow the difficulties and obstacles to deflect him from the target which he had set himself. People who knew him only slightly considered him shy, retiring, and a bit of a recluse. Maybe that was due to the way he handled a conversation, and perhaps to his desire to be left alone when pondering a problem. He greatly loved and was grateful for simple entertainment and distraction outside his scientific work, but he also was a man with unfailingly sharp and precise judgment on matters political, social and human. I do not think that Ehrlich ever made a decision unaware of what went on in the world around him; nor do I think that he ever gave anybody wrong advice. He was a thoroughly reliable friend and I keep his friendship in grateful remembrance."

Permit me to add just a few words to Ferdinand Blum's appraisal of Ehrlich. As I speak to you tonight, Ehrlich's personality and achievements have a very special significance to me also in another direction. I hope you will not think me presumptuous if I compare his work to the job which all of us have taken upon ourselves. With all his strength and all his heart Paul Ehrlich fought against the diseases of the body. We too are fighting—against the deadly dangerous disease of the mind emanating from the totalitarian school of thought. On this occasion we pledge ourselves to carry on this fight, confident to succeed.

THE ERA OF PAUL EHRLICH

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The era of Paul Ehrlich is the period in which Germany exerted a preponderant influence in the affairs of the world. Ehrlich was about seventeen years old when France was defeated by Prussia and the German states which Bismarck welded into a new Empire. When Ehrlich died, the first World War had just entered into its second year. Thus his manhood extends over the era of Bismarck and Wilhelm II, when Germany played the role of a world power, proud of her army and her "Kultur." In the wake of the Franco-Prussian War, the German university of Strasbourg was founded, largely with the aim of counterbalancing the French influence in Alsace. University professors were esteemed as perhaps never before, and the Geheimrat was almost a minor deity. It was a time of great achievements in all the sciences. All over the world, German had to be studied by scientists no less than by students of the humanities who wanted to keep abreast of new methods and results. If the professor was well aware of what others owed to his rank, he also remembered what he owed to his position: never ceasing hard work, thoroughness and self-criticism in his investigations, objectivity in viewing the results of others. It was the devotion to his calling that had raised the German professor to a pinnacle, not the mere worship of a title, widespread as such worship might be.

Yet achievement is not always identical with inner strength and greatness. The time of classical German philosophy and literature was a matter of the past. With some exceptions, the greatest names in the history of German sciences of the nineteenth century had made their debut prior to 1870. Among historians, Ranke was a very old man, and of Mommsen's Roman History the first three volumes had appeared in the late fifties. Liebig, the great chemist, died in 1873. Henle the anatomist, Virchow the pathologist, Helmholtz and Carl Ludwig the physiologists, the clinicians Frerichs, Traube and Wunderlich had long occupied chairs of their own. Altogether, the debates over fundamental philo-

sophical and scientific issues had lost vigor because of lack of opposing factions. To be sure, Darwinism was a lively topic, but its radical defense by Haeckel dated back to 1868. In 1872, Du Bois-Reymond read a paper "On the Boundaries of the Knowledge of Nature" which he concluded with the words: "Yet, when the Scientist finds himself confronted by the riddle of matter and force, and their ability to think, he is obliged once and for all to pronounce the most difficult of judgments: 'Ignorabimus'" [we shall never know].[1] Now what is left for the scientist in the face of such philosophical resignation? Research that will lead to positive results, especially those useful in human life.

Science and learning in the Germany of that period were not private affairs. Unless the individual found a position in a public institution, he remained an outsider. And public institutions were integrated into the state. Plans to establish a university in Frankfurt, the seat of Ehrlich's Institute, dependent solely upon the plans of its private founders, came to naught when the Mayor opened a meeting with a copy of the Statutes of the Prussian State in his hand and read: "The universities are creations of the State."[2] This state made itself felt in many respects as a protector as well as a supervisor. Virchow might defy Bismarck; among his younger colleagues a certain aloofness from politics, leaving this field to the ordained rulers, became widespread. The political events found a relatively weak echo at the universities. Professors and students alike mostly came from well-to-do homes. Students did not work their way through college and aspirants to an academic career needed private means while waiting for an appointment. Arbitrariness at the helm of the state bred arbitrariness lower down. In the Prussian cabinet for cultural affairs, Friedrich Althoff came to rule as a veritable autocrat. As Ehrlich's example shows, he could be of the greatest help in furthering talented men. But his treatment of professors dependent upon his approval did not help to strengthen their moral backbone. Moreover, the official policy of the state, Prussia as well as Germany, became anti-Semitic under the influence of Adolf Stoecker, the court chaplain in Berlin. It was an anti-Semitism that did not allow a Jew to become a full professor unless he was baptized. In medicine, particularly, the influence of the state went further than in many other European countries, let alone the United States. Public health found a central body in the Reichsgesundheitsamt, established in 1876. In 1880 Robert Koch was appointed to this organization which combined the functions of an insti-

tute for bacteriological and epidemiological research with a public health agency. That the state should have a hand in controlling drugs, especially vaccines that needed standardization and careful preparation, was almost a matter of course, as was the inspection of meat, isolation and disinfection in cases of infectious disease, compulsory smallpox vaccination of babies and school children, and the many other major and minor regulations where the paternalism of the state met with the national respect for administrative wisdom. When a scientific meeting was held at Königsberg, Virchow and a colleague of his took a walk along the coast, stomping with difficulty through the sand at the bottom of the dunes. They were hailed by some ladies suggesting that on this special occasion they take the easier though prohibited path on top of the dunes. Virchow not only refused but got angry and excited and continued stomping through the sand, holding forth about the lack of understanding among ladies for laws that served the common good and that had to be obeyed by everybody on all occasions.[3] From 1881, this paternalism of the state took a new departure when Bismarck initiated a program of social insurance that was to include compulsory sickness insurance as well.

It hardly needs saying that the government enforced its requirements for obtaining a license to practice medicine as a physician. This presupposed a secondary education with a strong classical note and a prescribed minimum of years of medical studies at a university. Certain courses, as well as a few official examinations, were required before the license was issued which was valid in all German states. The degree of M.D. was subject to the writing of a thesis and an additional oral examination. But it is the leeway that the German system of medical education allowed to the student which needs to be stressed in connection with Paul Ehrlich's development. Apart from the minimum requirements, the medical student was free to choose his courses, to change his universities, and to devote almost as much time to his studies as he desired. Anatomy, physiology, pathology, etc. were presented to him as sciences, each in its own right. If he felt attracted by any of them he was not only free to concentrate his energies upon it, but almost from the beginning it was made possible for him to engage in investigative work of his own. To the mediocre student, the absence of a rigid curriculum was a danger, often a temptation to waste years in idleness and an excessive consumption of beer. To the good student it was an opportunity to

find his own way, free from spoon feeding. Above all, it was an ideal training ground for future scientists. The system was based upon the identity of teaching and research and fostered a veneration for research which hardly found its equal anywhere else.

We characterized the time of Paul Ehrlich as the period of preponderant German influence, on a scene, we now have to add, where medicine became increasingly international. The formation of international societies and congresses falls largely within these years. The problems to be attacked and the methods to be used for their solution tended to become the same in all countries. This increasing uniformity was necessitated by the intrusion of exact scientific research into all fields of the healing art, including its practice.

Around 1860 there were as yet few skills which a good doctor could not have acquired from a practical course in gross anatomy, the example of a good preceptor, and books. The ophthalmoscope introduced by Helmholtz in 1851, and the laryngoscope invented by Manuel Garcia in 1855 were just coming into their own and might require additional training. As to the progress in pathology and experimental physiology—what was there that could not be followed by reading the literature? Changing concepts of disease were interesting but not of vital importance as long as they had little practical bearing. The first sweeping change, I think, came in the wake of Virchow's cellular pathology of 1858, with its transition from gross anatomical description to microscopic study. To anybody, untrained in the use of the microscope and not acquainted with normal histology, the new doctrines must largely remain ununderstandable. More important, perhaps, were the practical applications of microscopy which extended all the way from a reliable postmortem diagnosis to the examination of urine sediment. Here then was a need to learn a whole new branch of science, not only an isolated technique as, for instance, cystoscopy. The experience of William Welch who went to Strasbourg to study pathology and had first to take a course in normal histology with Waldeyer illustrates our point.[4]

Microscopy owed a good deal of its progress to improvements in staining of specimens. In the fifties, von Gerlach had popularized the use of carmine as a stain. Julius Cohnheim under whom Carl Weigert spent many years in Breslau and in Leipzig, and who for some time was Ehrlich's teacher, was one of the masters in the development of staining methods. Cohnheim used gold chloride and aniline blue in his famous

studies on inflammation of 1867.[5] Leukocytes ingested aniline blue that had been injected into the blood stream; they were thus tagged and their appearance in inflamed tissue proved that they had found their way through the walls of the blood vessels and were identical with the pus corpuscles. This epoch-making paper of Cohnheim's is worth mentioning not only as an example of the interest in staining methods but also because it played a part in the controversy between the two leading pathological schools in Germany. Cohnheim's investigation centered around keratitis and demonstrated that here too the changes in the blood vessels —at the periphery of the cornea—are the first phase of inflammation. Thereby he contradicted Virchow on a point of great theoretical importance.[6] Without personal animosity, the differences between the two were yet to develop into an opposition between the morphological and experimental schools. To Virchow and his pupils pathology, that is the study of disease, was becoming more and more pathological anatomy;[7] to the adherents of Cohnheim it meant, above all, physiology and experimentation. The difference was really one of emphasis rather than excluding principles. However, it seems that Cohnheim and his circle stood closer to the rise of bacteriology. And the emergence of this new science, even more than pathology, forced the practitioner to abandon the old ways and to keep step with scientific progress.

The debt which bacteriology owes to Pasteur is so well known that we need not dwell upon his early work. Around 1876 the question was not so much whether microorganisms could cause disease; rather it was which diseases are caused by microorganisms and how can claims in this direction be proved.[8] The answer to the latter question was given by Robert Koch's famous postulates. It took a longer time to survey the domain of infectious diseases; it is not quite surveyed even now. Nevertheless, in 1882 when Koch announced his discovery of the tubercle bacillus, the immediate value of bacteriological techniques could no longer seriously be doubted, where the diagnosis of relapsing fever, anthrax, actinomycosis, gonorrhea, leprosy, typhoid, malarial fever, and tuberculosis was concerned. It goes without saying that the correct diagnosis often had its immediate consequences for prognosis and prophylaxis. This meant that a physician could not be satisfied with reading in books about the progress of bacteriology; he had to be able to handle the new methods required or at least to be able to avail himself of expert services. The speed with which one new discovery followed an-

other must have contributed to the growing sense of a changing time. Two years later, in 1884, diphtheria, cholera, tetanus had been added to the list and, at the same time, antiseptic surgery was constantly gaining new triumphs.

Antiseptic surgery did not presuppose much bacteriological refinement. It rested on the simple assumption that surgical infection was carried to the wound by hostile microorganisms that could be destroyed by a chemical agent, carbolic acid. This assumption almost strikes us as too simple. But the anecdotes about the surgeons who, after careful antiseptic preparation, continued to operate with a scalpel that had fallen to the floor, and similar stories indicate that to the generation of the seventies and eighties a great effort was needed to grasp the underlying principle. That we think of Lister's teaching as simple merely goes to prove how different the outlook of younger men who, like Ehrlich, grew up with the changed views must have been from that of the generation before him.

Antiseptic surgery, which in the nineties was to be succeeded by aseptic surgery, made the healing art more efficient in its cure of disease. For a number of years surgery seemed superior to internal medicine. *Circumstare et verba facere,* to stand around and talk, was all the internist seemed to be able to do while the surgeon snatched people away from imminent death by boldly removing an inflamed appendix or a cancer of the stomach. Therapeutic successes of internal medicine were relatively slow to come because they needed an elaboration of so many factors: immunology, experimental physiology, and pharmacology. Though many of the results were achieved later, the foundation nevertheless was established during the years under discussion.

As with the rise of bacteriology, so with immunology the name of Pasteur is intimately connected. In 1879 he discovered the possibility of immunization against infectious disease by attenuating the culture of the responsible virus. This discovery led to great practical results; but the physiology of immunity remained dark. Two theories arose in short succession seemingly excluding each other. Metchnikoff made "phagocytosis" the main line of defense; harmful particles were removed by cells that acted the role of policemen. However, this theory was not adequate to explain protection against dissolved toxic substances; here a humoral theory looked more promising and the promise found an early fulfillment in von Behring's invention of antitoxic sera for tetanus and

diphtheria. But this brings us so close to the borderline of Ehrlich's own contributions that we had better turn to another aspect of developments in internal medicine.

In a paper of 1878, Julius Cohnheim made an attack directed, as I believe, against men like Brown-Séquard and Claude Bernard,* although he did not mention the great experimental physiologists by name.[9] Cohnheim claimed that experimental pathology should be in the hands of clinicians who encountered disease at the bedside or pathological anatomists who studied its appearance on the postmortem table. The physiologist, because lacking the necessary contact with morbid phenomena, would tend to raise and answer physiological questions. I do not know whether Cohnheim actually had in mind Claude Bernard's *Introduction to Experimental Medicine* that had appeared in 1865. But his attack is understandable from the point of view of German conditions. Much of what this book was fighting for had become reality in Germany. Not only pathologists like Cohnheim, but clinicians too combined the clinical, anatomical, and experimental approach. As examples we may choose Frerichs and Traube who represented internal medicine at Berlin—in disharmony we must say, for they were bitter personal enemies. Now Traube is usually remembered as one of the founders of German experimental pathology. As far back as 1846 he had declared that "it is the experiment, added to passive observation, which can make pathology too what it wishes to become, an exact science."[10] But it is not always remembered that Frerichs also was an experimentalist. As a young professor he had become famous through his article on "Digestion"—a purely physiological subject—and shortly afterwards his work on kidney disease that utilized animal experiments. More than Traube, Frerichs was also versed in chemistry.[11] One of his greatest pupils, Naunyn, tells us about Frerichs' attitude towards his assistants of whom Ehrlich later was to be one. "He accepted each one from the very first day as a man who unquestionably could and would do everything the position required of him. So confident was he, unfortunately, of this that he never gave us any instructions as to how we should do anything; indeed, he scarcely said what he wanted done, and he actually managed to have everything done to his satisfaction without any such explana-

* Cohnheim's attack only mentions "the chairs and institutes for experimental pathology which, in a neighboring state, exist at several universities." As far as I can see this would fit France, where Brown-Séquard held the chair of "Comparative and Experimental Pathology" in Paris from 1869 to 1872 to be succeeded by Vulpian, 1872-1887; cf. Prévost, A. *La faculté de médicine de Paris.* Paris, A. Maloine, 1900, p. 46f.

tions." A little later on Naunyn adds: "It was just as much a matter of course that we should make scientific investigations and produce able pieces of work, as that we should perform our clinical duties to his satisfaction. What this work should be and how we did it was again entirely up to us, for he let us come and go and do whatever we wished, however we wished."[12] It is only necessary to point out that Naunyn in turn had as his pupil Minkowski whose work on the pancreas and diabetes was one of the preconditions for the discovery of insulin, in order to perceive the clinical tradition of the Frerichs' school in which chemistry and animal experiment combined with pathology to render medicine scientific.

We might expect that the search for exactness in medicine would lead such a school to therapeutic nihilism which had plagued medicine around the middle of the century. But this was hardly the case. Frerichs, a consultant with a very large clientele, was saved by his faith in "proved" remedies from falling into the pitfall.[13] The younger generation was saved by association with experimental pharmacology. Historically speaking the new pharmacology stemmed from the same root as experimental medicine; it really was a part of the latter. In 1873 there appeared the first issue of the "Archives for experimental pathology and pharmacology"[14] edited by the clinician Naunyn, the pathologist Klebs, and Schmiedeberg, professor of pharmacology. The first three articles are characteristic: an investigation of blood coagulation in the living animal; a discussion of the effect of quinine on blood; and a contribution to the knowledge of micrococci; even the budding discipline of bacteriology was represented.

The nature of the new pharmacology needs a word of explanation. Schmiedeberg, in his textbook, defined it as "the science of the changes brought about in the living organism by chemically active substances, except foodstuffs, without regard as to whether such substances are used for curative purposes or not."[15] In other words, the pharmacologist merely investigates "the living processes under the influence of drugs."[16] He is a biologist. It is up to the physician then to choose those drugs he wishes to use in therapy. Pharmacology and materia medica stand in the relationship of a pure science and its application. The science exists regardless of its application, while application should not be made without the backing of science.

We characterized the time of Ehrlich as one of achievement. We

set out to trace its general features and then tried to sketch the situation in medicine during Ehrlich's formative years. It was a peaceful time that allowed a man to concentrate on the work at hand, sometimes without looking up and seeing wider horizons. To unravel the mechanism of things may have occupied the mind more than to know their interconnection. As has been pointed out, public health was submerged by bacteriological studies[17] and medicine treated man as an organism with little soul inside.* Yet the end of our survey showed a belief in the superiority of science over its applications, and in conclusion we may ask what this belief embodied. We shall try to solicit the answer from the Englishman, Thomas Huxley, who became something of a philosophical spokesman for many biologists of the late nineteenth century. In an address of 1866, Huxley[18] looked back upon the great pestilence that had ravaged London about 200 years before. "Surely," he exclaimed, "it is true that our countrymen are less subject to fire, famine, pestilence, and all the evils which result from a want of command over and due anticipation of the course of Nature, than were the countrymen of Milton; and health, wealth, and well-being are more abundant with us than with them?" Remembering the repeated epidemics of Asiatic cholera and typhoid, the high incidence of tuberculosis and venereal disease which then prevailed we might not grant a positive answer with the assurance Huxley expected. However that may be, the speech goes on to say that in the eyes of many contemporaries, natural knowledge is nothing "but a sort of fairy godmother, ready to furnish her pets with shoes of swiftness, swords of sharpness, and omnipotent Aladdin's lamps, so that they may have telegraphs to Saturn, and see the other side of the moon, and thank God they are better than their benighted ancestors." To which Huxley contemptuously replied: "I think I would just as soon be quietly chipping my own flint axe after the manner of my forefathers a few thousand years back, as to be troubled with the endless malady of thought which now infests us all, for such reward."[19] The "practical benefits" as he calls them are but incidental. "I say that natural knowledge, seeking to satisfy natural wants, has found the ideas which can alone still spiritual cravings. I say that natural knowledge, in desiring to ascertain the laws of comfort, has been driven to discover those of conduct, and to lay the foundations of a new morality."[20]

* Although the beginnings of psychoanalysis fall within the 1890's, it was of relatively little influence before the first World War.

We may no longer share such a robust faith in the spiritual value of natural science. Nevertheless, we have to recognize it as an expression of the striving of many scientists in the time of Paul Ehrlich. It was the existence of such faith that made them value their work beyond the immediate results they achieved.

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PAUL EHRLICH—MAN AND SCIENTIST

ERNST JOKL

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May I open this discourse by reading to you a letter received a few days ago from Sir Henry Dale in London:

Dear Dr. Jokl,

"I shall myself be attending, on March 14th and 15th, the celebration which has been organized in Frankfurt to commemorate the centenary of the births of Paul Ehrlich and Emil von Behring. I gladly accept your invitation to send to the Commemorative Meeting at The New York Academy of Medicine an expression of my veneration for the memory of Paul Ehrlich. More than any other man, I think, Ehrlich was responsible for the tremendous revolution in the medicinal treatment of disease which has taken place during the last half century. He had a large share of the responsibility for making immunology a progressive, experimental science. In retrospect, however, his immunological work appears to have been a diversion from, or an opportunist extension of, the main line of his researches. Even from his student days, his mind appears to have been permeated and his activities directed by the idea of a therapeutics based upon specific chemical affinities; and the line of development appears to be direct, from Ehrlich's early work on the use of dyes as micro-chemical reagents, and on the oxygen-needs of the tissues, through salvarsan to the sulphonamides, the antibiotics, and all the great modern wealth of directly curative remedies.

I myself have personal memories of Ehrlich's endearing personality, and I gladly join with you in celebrating the centenary of the birth of this great man of genius, and great benefactor of mankind."

Sincerely, — H. H. Dale

Ehrlich was appreciated during his lifetime and indeed received a great deal of recognition, scientific as well as personal. Willstatter, the great chemist, describes in his autobiography how Ehrlich in the last years of his life was persona gratissima with the German Kaiser, and that the strict ceremonial of the Imperial Court did in no way apply to him. However, the working of his mind and the nature of his research were so original that their significance was not immediately understood.

In a letter, Professor Aschheim, the co-discoverer of the pregnancy test, refers to this fact. He writes:

"I attended several lectures Ehrlich gave in Berlin. His discourses were always received with enthusiasm notwithstanding the fact that many among his audience were unable to follow his ideas. It was his custom to ask during his lectures, 'isn't everything perfectly clear?', and everybody shouted, 'Yes, yes'. Who indeed would have admitted to the kind professor that his theories were in fact quite difficult to grasp?"

Today, almost forty years after his death, we are in a better position to draw a picture of the man and the scientist who, as Sir Henry Dale points out, was responsible for the tremendous revolution in the medi-

cinal treatment of diseases which has taken place during the last half century.

Ehrlich's life and his work are characterized by three axiomatic trends of thought. The first of these is that Ehrlich thought in quantitative terms. The second is that he possessed the gift of formulating dynamic, scientific hypotheses which he presented picturesquely as if he were to describe mechanical models. The third is that the leitmotif for Ehrlich's research work was the theory of his teacher, Julius Cohnheim that natural adaptations in pathological processes are unreliable.

As to the first axiom, I quote a paragraph from James Clark Maxwell's "Theory of Heat" to which Ehrlich has frequently referred:

> "The most important step in the progress of every science is the measurement of quantities. Those whose curiosity is satisfied with observing what happens have occasionally done service by directing the attention of others to the phenomena they have seen; but it is to those who endeavor to find out how much there is of anything that we owe all the great advances in our knowledge. Thus every science has some instrument of precision, which may be taken as a material type of that science which it has advanced, by enabling observers to express their results as measured quantities. In astronomy we have the divided circle, in chemistry the balance, in heat the thermometer, while the whole system of civilized life may be fitly symbolized by a foot rule, a set of weights and a clock."

If Ehrlich would have done nothing else than introduced into medical research the principle of measuring, he would have left his mark. This point is well illustrated in the citation of his Nobel Prize in 1908. At that time Ehrlich had not yet started his work on chemotherapy which was to lead to the discovery of salvarsan. Professor Liljestrand of Stockholm, who has reviewed the story of "The Nobel Prize in Physiology and Medicine," writes as follows:

> "Important contributions to the interpretation of the immunity process were made by PAUL EHRLICH (1854-1915). In 1891 he succeeded, for instance, in making test animals immune to certain vegetable poisons (abrin and ricin) and defined the degree of immunity as the ratio between the largest amount of poison an immunized animal can stand and the dose that would kill an untreated one. To develop fully the power of resistance to a poison, a latent period is required, as shown by the fact that the resistance power of the test animals suddenly becomes increased on the sixth day after injection, the degree of resistance depending on the amount of poison injected. When the doses were gradually augmented, a correspondingly greater quantity of antitoxin was produced until there was toleration of several hundred times the amount of poison that would originally have been fatal. While the active immunity thus obtained was not hereditary, it could be transmitted to the offspring by the mother's milk. The application of these results to the production of effective sera has been of outstanding practical value. The same is true of the method devised by Ehrlich to determine biologically the strength of a diphtheria serum. In this test the basic immunity unit is taken to be the amount which in a guinea-pig weighing 250 grammes is able to neutralize one hundred times the amount that would ordinarily cause death.

"The introduction of quantitative methods in immunology caused Ehrlich to attempt an explanation of the immunization process. His conclusions were embodied in his celebrated 'side-chain' theory. Since the antitoxin has a much larger molecule than the toxin, it cannot be a derivative of it, he argued, but must be produced by the living organism's reaction to it. The toxin he supposed to contain special so-called haptophorous groups by which it can be bound to certain cell elements which Ehrlich called receptors, corresponding to the 'side-chains' attached to a benzene ring. These elements are consequently neutralized and made useless for their ordinary metabolic purposes. In the toxin there are, furthermore, so-called toxophorous groups, and with their aid the absorbed agent can attack the cell directly. If the cell survives the attack, new receptors are formed, and, as often happens under extreme strain, the reaction creates a surplus of them; some of the superfluous receptors are then discharged into the blood and the tissue fluid in which they are able to absorb and neutralize the toxin. In certain cases (bacteriolysis, haemolysis) this does not happen until after the immune bodies have become fused with still another element (complement). Just as iron rods, when placed outside a house, can protect it against lightning, while the same rods set up inside it can have the opposite effect, so the receptors, once they have been ejected from the cell, can have a protective influence, whereas inside it they would have increased the effect of the toxins. Between the toxin and the antitoxin Ehrlich assumed that there was a relatively stable chemical relationship.

"A certain amount of criticism has been directed at some aspects of Ehrlich's 'side-chain' theory, especially by S. Arrhenius and T. Madsen, particularly in reference to the relationship between the toxins and the antitoxins, but as a working hypothesis it has undoubtedly had a considerable value. Within the Nobel Committee too, doubts were expressed but a majority was of the opinion that Ehrlich's contributions to immunity research were so outstanding that they deserved a prize. As a matter of fact, since the year 1901, Ehrlich had been nominated about seventy times from thirteen different countries. While by some of his sponsors such achievements as his creation of modern clinical haematology and the discovery that the tubercle bacillus is acid-fast had been cited as arguments for an award, a majority of the nominations were based on his works on immunology. The attitude of the Committee regarding the latter was identical with that of one of his supporters (C. J. Salomonsen) who wrote: 'Whatever one may think of his side-chain theory, there can be no doubt that, since the death of Pasteur, Ehrlich has been the foremost worker in the entire domain of immunology.' Being in accord with that opinion, the Institute awarded one-half of the prize for 1908 to EHRLICH 'in recognition of his works on immunity.'"

During the years between the award of the Nobel Prize in 1908 and his death in 1915, Ehrlich reaped the fruits of his insistence upon measurement in medical research. The classical experiments in which he tried to increase the efficacy of chemotherapeutic substances of known pharmacological trends while at the same time endeavoring to eliminate their toxic side effects were altogether based on this principle. On p. 589 of the Festschrift published on the occasion of Ehrlich's 60th birthday, Hata and Shiga presented a diagram showing exactly the toxicity ranges of salvarsan as against neo-salvarsan. This diagram represented a model for the conduct and presentation of experiments in chemotherapy and pharmacology. In conformity with Maxwell's criteria of scientific procedure, Ehrlich had succeeded in creating a technique of

precision "which may be taken as a material type of that science which it had advanced, by enabling observers to express their results as measured quantities."

As to the second axiom, viz., that of formulating scientific hypotheses as if they were mechanical models, Professor A. V. Hill of London recently said that: "facts alone are apt to be dull things and need to be tied together by theories or applied to practical problems if they are to be made reasonably palatable." And during the last quarter of the 19th century, Lord Kelvin taught in Glasgow that "you cannot have clarity on a scientific concept before you have presented it in form of a model."

The significance of Ehrlich's models must be judged not only from the heuristic value they had for himself and his pupils, but equally so from the fact that until today they have not lost vividness and dynamic quality. I refer to the theories of the "side-chains," of the antigen-antibody-complement pattern, of the "lock and key" symbolism with which he explained the toxin-antitoxin interaction, and of course to the magic bullet, the "zauberkugel" with which he "shot" at pathogenic microorganisms, so as to bring about the therapia sterilisans magna.

As an example of Ehrlich's picturesque presentation of scientific ideas, I quote from his first major work "Das Sauerstoffbedürfnis des Organismus".

> "Exactly how the dye gets into the cell I am not yet sure, but there can be no doubt that its entry into the cell is dependent on the size of the molecule. I imagine it must be so. Just as meteors penetrate into the gaseous atmosphere of the earth, so molecules of the smallest size are projected into the plasma of the cell and remain there, useful in some way or another (as oxygen-carriers for instance), and then are again eliminated."

On another occasion he wrote:

> "I can picture the chemical formulae in my mental vision and I believe that this fact has been of the greatest value to me in my studies. I had foreseen many things in pure chemistry which came to be known much later."

At the time of the award of the Nobel Prize in 1908, Ehrlich's work on chemotherapy had not been started. I shall read to you another passage from Professor Liljestrand's book in which the little known fact is revealed that, if Ehrlich would have been spared a few more years, he would in all likelihood have been awarded a second Nobel Prize in recognition of his discovery of salvarsan.

> "The pioneer in chemotherapeutic research was Ehrlich. When he made his famous investigations of organic arsenic compounds, he could base them, among other things, on P. Uhlenhuth's observation that atoxyl was both a preventive and a remedy for experimental trypanosome and spirilla diseases, and that it also had

a beneficial effect on syphilis in human beings, even if its high toxicity made its use impracticable. Ehrlich then analyzed the composition of atoxyl and subsequently produced a large number of different arsenic preparations which he tested on animals suffering from experimental syphilis. These extensive and laborious investigations, which were made in cooperation with S. Hata, led as is well known, to the introduction of salvarsan (arsphenamine) and neo-salvarsan (neoarsphenamine) as a specific against syphilis and a number of other infectious diseases caused by trypanosomes or by spirochaetes. The results were highly sensational. Although Ehrlich had already received a Nobel Prize in 1908, *he was again nominated* in 1912 and 1913. That his new achievements were not, however, submitted to a special investigation was only natural, since practical experience was still too limited to determine the value of the remedy in the treatment of syphilis, which, of course, was the most important consideration. Because of Ehrlich's death in 1915, the subject was not taken up again; it is now generally admitted, however, that this contribution must be regarded as a landmark in the development of chemotherapy."

The third axiom of which I have spoken, matured early in Ehrlich's career, while he was still a student in Breslau. At that time he was profoundly impressed with the teachings of Cohnheim to the effect that natural adaptations in pathological processes are unreliable.

Before elaborating this point, I must refer to the richness of scientific life in Breslau in the 70's and 80's of the last century. Three great men of this period in particular left their mark upon Ehrlich's mind. The first was Ferdinand Cohn, next to Linnaeus the greatest botanist of all times; a brilliant and kind man, the first biologist to understand the categorical significance of the then newly discovered world of microorganisms; the last encyclopedist of his scientific discipline which since has grown so much that no individual can ever hope to master it in its entirety; and of course, I must mention that Ferdinand Cohn was the discoverer and sponsor of Robert Koch. The second great man of the Breslau period of Ehrlich was Rudolf Heidenhain, successor to the Chair of Physiology of Purkinje, teacher of Pavlov, who worked under him and who wrote in Breslau under Heidenhain's guidance, his first scientific paper. Thirdly there was Julius Cohnheim whom the late Simon Flexner has rightly described as the greatest pathologist of all times. Since his esteemed cousin, Carl Weigert, was Cohnheim's assistant, Ehrlich was very close to Cohnheim's ideas.

Ehrlich was privileged to be taught by these three men. From Ferdinand Cohn he learned how to formulate lively scientific hypotheses and to think in terms of models; from Heidenheim he learned how t measure quantities in biology; and Cohnheim convinced him that in it adaptive reactions to pathological impacts nature is unreliable. As to this point it is indeed fortunate that we have at our disposal the account

which William Henry Welch gave of the teachings of Cohnheim whose assistant he was in Breslau. In 1939 Henry Sigerist made us indebted to him by publishing a new edition of William Henry Welch's address before the 1897 Annual Congress of American Physicians and Surgeons in Philadelphia, entitled "Adaptation in Pathological Processes." In this address Welch, who had then returned from Breslau to this country, explained how

> "Colnheim did not regard pathology as a static, recording science, as most of his contemporaries did. He sought comprehensive theories to interpret the ever-increasing volume of unconnected facts as experimental and anatomical research revealed them. 'Adaptation in pathological processes' he said, 'cannot be looked upon as bringing about rational adjustments to the changed conditions created by a causative pathological event.' He stressed his belief that one fails to see in pathological adaptations 'that co-ordinate and special fitness which we are accustomed to find in physiological adaptations.'
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> "In order to illustrate his arguments, he first subjected to an analysis the pathological process of compensatory hypertrophy of heart muscle. He arrived at the same result as had been reached before him by Nothnagel, namely, that 'no teleological idea or form of language need enter into the explanation of the mechanism of the process.' Pathological reactions, he maintained, may or may not be of 'therapeutic' significance. Frequently they even greatly aggravate the seriousness of the case, as he exemplified in the case of certain clinical aspects of inflammation: — —
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> "The more severe and extensive the inflammatory affection, the more serious, as a rule, is the condition of the patient. The surgeon sees his wounds do well or ill according to the character and extent of inflammatory complications. Measures directed to the removal of inflammatory exudation, such as the evacuation of pus from an abscess or an empyema, are the most successful methods of treatment, and the rules are embodied in ancient surgical maxims. How can one conceive of any purpose useful to the patient served by filling the air-cells of his lung with pus-cells, fibrin and red corpuscles in pneumonia, or bathing the brain and spinal cord in serum and pus in meningitis? The closure of pathological defects by new growths of tissue is a process which must be regarded as adaptive. But one would hardly describe as advantageous the scar in the brain which causes epilepsy. If nature has no better weapons than those to fight pneumococcus or meningococcus, it may be asked, what is their use but to drive the devil out with Beelzebub?"

Up to the time of his Nobel Prize, Ehrlich had hoped to develop the revolutionary method of treatment, the therapia sterilisans magna of which he had dreamed since his youth, by adjusting, manipulating, and improving the very weapons which nature itself uses. When von Behring discovered the diphtheria antitoxin, it was Ehrlich who realized that in concentrations in which nature produces this substance, its therapeutic potency would be limited. He therefore set about to make antitoxin available in very much higher titers. There is scarcely a normal immunological phenomenon whose therapeutic potentiality Ehrlich had not tried to utilize; but it was only during the last years of his life when he relied altogether on non-natural, non-physiological substances,

on aniline dyes, on metals and on chemicals of all sorts, that he succeeded in producing his "magic bullets." The direct line of development from "Ehrlich's early work on the use of dyes as micro-chemical reagents," of which Sir Henry Dale writes in his letter, "and on the oxygen needs of tissues, through salvarsan to the sulphonamides, the antibiotics, and the great modern wealth of directly curative remedies;" this line represents the ultimate application of Cohnheim's thoughts. Of course, Cohnheim himself had been influenced by Virchow, and Virchow by Rokitansky. Still, the laurel belongs to Ehrlich.

I like to refer to an analogous situation in the world of music to which Sigmund Spaeth has drawn attention, a situation in which a master chose to devote his genius to the perfection of an idea which had matured before his time.

> In the St. Matthew Passion, written for a Good Friday service in Leipzig, Johann Sebastian Bach made striking use of the chorale, O Haupt voll Blut upd Wunden (O Sacred Head now wounded), which occurs five times in the course of the work. This seems to have been his favorite of all the Lutheran hymn tunes that came out of the old German folk-music, for he used it again in his Christmas Oratorio, with the words Wie soll ich dich empfangen? (How shall I then receive Thee?), a regular Advent hymn, to which he evidently wished to give a touch of Lenten prophecy. It also appears in four of Bach's cantatas and in his Choralgesange.
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> This wonderful melody fully deserved such attention. It was known first in 1601, as a secular love-song by Hans Leo Hassler, Mein G'mut ist mir verwirret von einer Jungfrau zart (My spirit is distracted all through a maiden fair). Neither Martin Luther nor Johann Sebastian Bach was inclined to overlook good music merely because its sentiments might not be entirely religious. In 1613 Christoph Knoll had already made a hymn of the lovesong, beginning "Herzlich thut mich verlangen nach einem sel'gen End." ("My longing is most hearty toward a blessed end.") In 1620 a poet named Schneegass changed the words to "Ach Herr, wir armen Sunder" ("O Lord, all we poor sinners"), and in 1656, still nearly thirty years before Bach's birth, Paul Gerhardt established the song as a Lenten chorale, with the words that now appear in the Lutheran hymn-books and in the St. Matthew Passion.

Ehrlich was an impressive personality notwithstanding the fact that he was modest and certainly did not set out to impress. A great number of his contemporaries have dealt at length with their reminiscences of him. I have quoted to you Sir Henry Dale and Professor Aschheim. I have received a delightful appreciation of Ehrlich from his distinguished publisher, Dr. Ferdinand Springer in Heidelberg who earned Ehrlich's special gratitude by sponsoring the fine biography of his cousin Carl Weigert whose scientific excellence was, to Ehrlich's sorrow, not reflected in his academic advancement. Dr. Springer also placed the resources of his publishing house at Ehrlich's disposal when together with Dr. Hata the manuscript of his book "Die experimentelle

Chemotherapie der Spirillosen" was completed, and he published the biography of Ehrlich by his former secretary, Miss Marquardt.

Dr. Chaim Weizman in his book "Trial and Error" writes at length of a meeting with Ehrlich. Friedrich von Müller, the celebrated Munich internist, devotes a warm personal reference to him.

Many valuable links exist between Ehrlich and this country. Landsteiner and Michaelis, his master pupils, worked for many years in New York. Ehrlich's daughters and his gifted grandchildren, Dr. Hans Wolfgang Schwerin and Mr. Gunther Schwerin actually live in New York. I have enjoyed the friendship of the Schwerin family since my childhood and I remember with pride, that I met Ehrlich shortly before his death in their hospitable home in Breslau. Ehrlich's cousin, and devoted co-worker, the great dermatologist, Professor Felix Pinkus, came to this country in 1940. He died in Detroit where his son Herman continues in the footsteps of his father. The nephew of Professor Edinger, the neurologist, one of Ehrlich's closest friends of his Frankfurt period actually is today with us. I refer to the Consul General of the West German Republic, Dr. Hans Riesser, whose brother Otto was a pupil of Ehrlich.

When Ehrlich died in 1915 Professor Arnold Berliner wrote a memorable obituary in the "Naturwissenschaften" of September 3rd, which concluded as follows:

> "At dawn of history," so Goethe tells us, "men held a solemn and sometimes terrifying belief. They imagined their ancestors seated in silent communion in great caves in a circle of thrones. When a new soul entered this company, they would stand and bow to welcome him if he was worthy enough. The ancestors are the great men whose services to humanity are recorded in the Book of Eternity. We can be sure that they will bow deeply in profound veneration to the man now entering their presence."

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PAUL EHRLICH IN CONTEMPORARY SCIENCE

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IT WOULD be difficult for any student of Ehrlich, or of those subjects to which he dedicated his life, to surpass in clarity and understanding the obituary written by Neisser, a devoted admirer and assiduous co-worker. He wrote: "The fact is outstanding and wonderful, that Ehrlich understood from the beginning of his career the broad and useful application of a simple principle of basic biology. This held unerringly true throughout the work of his entire life in many apparently unrelated areas of science. It applied in studies of the form and function of cells and tissues, of biochemistry and immunology, of the nature of neoplastic growth, and finally, its most fruitful expression, in the creation of chemotherapy. The principle was so simple, so basic, and so obvious, that it is almost incredible that it was wholly revolutionary two generations ago. Even more incredible is the fact that it is so generally overlooked today.

"Everything that Ehrlich did was based on the concept of specific relationships between the molecular configuration of substances acting on cells and the constitutional elements of the structure of those cells. The logical sequel to this concept was the possibility of penetrating the most obscure details of cell life and function by the observations of the relationship of protoplasm to chemical units of known configuration. This was obviously the beginning of modern cytochemistry.

"The sentence of Ehrlich, 'Corpora non agunt nisi fixata,' expressed this principle as a law which governed not only the distribution of compounds according to their chemical constitution, but also their biological effects. From this law came inevitably the concept that a desired therapeutic effect could be obtained by virtue of a predetermined construction of a particular compound. This in turn led to the conclusion that the constitution of a potentially therapeutic chemical could be so formulated as to be fixed only by certain types of cells and so to affect them

specifically. These might be either cells of the body or invading cellular units such as bacteria."

Chemistry, up to Ehrlich's time, had simply provided an arsenal for the therapist, filled with substances from which the physician, with more or less luck, might draw a more or less useful weapon; it was converted by Ehrlich into the servant of the therapist who knew the details of his target and could formulate his chemical weapon rationally to achieve a predetermined end result.

Perhaps the most pertinent characteristic of Ehrlich's life was his pervading interest in color. Beyond all question, the Ehrlich monomania for the dyeing of tissues and his explanation of the mechanisms of this action, with his extension of it to explain biologic phenomena, epitomized this man's entire scientific career.

As a student, Ehrlich devoted most of his time to the study of staining reactions. His graduate thesis was written on this subject. As a young internist, from 1878 (at the age of twenty-four) to 1885, when his chief, Frerichs, died, he spent every spare moment in one or the other aspect of this work. During that period, in effect, he created modern hematology by his ability specifically to stain the various formed elements of the blood. Furthermore, he pursued this study not only as an end in itself, but to achieve a more adequate understanding of disorders of blood formation. In this work he gave us perhaps the first adequate description of pernicious anemia and aplastic anemia. He understood that while both were maturation defects, they were at different levels and of different types. He did not comment extensively on leukemia, and it is surprising that we find so few references in his work to the staining of neoplastic tissues. Both topics were studied, but an interest in them was overshadowed by the convention of the time, which directed practically all medical and scientific opinion to the bacteriologic etiology of disease.

When Koch's discovery of the tubercle bacillus was announced in 1882, it was natural for Ehrlich to recall the curious forms he had observed in tuberculous tissue stained with methylene blue. It was unavoidable that his inquiring mind should drive him back to a re-examination of similar tissues by new staining techniques, with a consequent discovery of acid fastness and the usefulness of aniline. It is nevertheless startling that this technique, now sixty-five years old, still stands as the best one available. It was during this period that he effected the mental

transition from the study of dead and fixed tissues to vital staining, an indication of his growing conviction that staining specificity was a tool which could be applied usefully to the investigation of biological processes.

His demonstration that methylene blue would stain nervous tissue specifically is well known, as is the fact that this technique pushed forward the whole study of neuro-anatomy. Few recalled, however, his immediate attempt to transfer this knowledge to a therapeutic objective. This was his effort to treat with methylene blue the dysfunctions of nervous tissue, then classified under the general term "neuralgia."

His next step, however, is hard to understand, unless one is prepared to assume either the existence of a vast number of unpublished studies or, on the part of Ehrlich, a much greater familiarity with the problems of the new German nation pushing for colonial expansion than he is commonly credited with possessing. In any event, he made a serious effort to use methylene blue in the treatment of malaria. Exactly why this disease was selected remains a mystery. It does seem certain, however, that some therapeutic effect was exerted, and this fact may well compose the cornerstone upon which the scientific effort of the remainder of Ehrlich's life was erected. The truth of this supposition is the more likely in view of the fact that the dominant characteristic of the man was his inability to forget anything or give up anything.

While serving as assistant to Gerhardt from the time of Frerichs' death in 1885 to 1888, Ehrlich was very unhappy. It was during this period that he developed the pulmonary tuberculosis which forced him to take a cure for two years in Egypt. He returned in 1889, the year of high enthusiasm about the possibility, advanced by Koch, of the treatment of tuberculosis with tuberculin. It was natural for the physician-patient to give the closest attention to this development. As far as one can judge, he never acknowledged a loss of faith in tuberculin therapy, although he was not sure of its effect in his own case. One must assume that as a member of Koch's staff, which he joined in 1890, he felt that loyalty to his chief precluded any expression of criticism, even though justified.

Koch had gone into bacteriology through Lister's influence, and this inevitably involved an interest in disinfection. One must presume from existing evidence that the shift of the concept of contact sterilization by phenol or mercury salts to that of internal disinfection (chemo-

therapy) was Koch's great contribution, and one exerting a profound effect on Ehrlich. It led, furthermore, to work by Koch, during his association with Ehrlich, on the definition of the chemical specificity of bacteria as manifested by their differential sensitivities to different chemical agents. To Ehrlich this could only mean the possibility of the chemical cure of bacterial disease.

In any event, it is probable that the failure of tuberculin therapy led Ehrlich to his first great contribution—the use of specific antitoxins in treatment. Roux and Yersin had described diphtheria toxin in 1888. As far as one can tell, von Behring and other workers in the field followed rather passively the Pasteur trend in emphasizing the study of active immunity to diphtheria. Ehrlich, presumably with Koch, saw that passive immunity might provide an active therapeutic approach, but that to achieve this end would require better quantitative methods and better antitoxins than were then available. At the time, the factors controlling the production of toxin were little understood, and every batch of antigen varied in strength. Consequently, efforts to develop a high-potency antitoxin were not productive.

This led to the establishment of a most basic contribution by Ehrlich—the standardization of procedure. Rather than undertake the immensely complicated task of working out the variable factors controlling toxin production by bacteria, he turned to a pure antigen, ricin. The use of this material gave the first clear evidence of antibody production to a non-bacterial antigen, led to an interest in drug resistance, and gave rise to techniques which made possible the production of high-titer diphtheria antitoxin useful in therapy. Furthermore, this work gave rise to the "side chain theory" with its two cardinal principles: 1) the requirement that a biologically active compound be fixed to its target cell in order to carry out its action; and 2) that the fixing units are produced in excess by the target cell, if it survives, to constitute the circulating antibodies.

One must assume that Ehrlich's ten years of work at the State Institute of Serum Research, from 1896 to 1906, saw the gradual development of his interest in the problem of neoplastic disease and a steady reinforcement of the conviction that specific chemicals could be found which would exert specific biological effects of a therapeutic nature.

It appears that the final conviction of the possibility of chemotherapy came to Ehrlich during the celebrated trip to the Society for

Internal Medicine, about 1890. At this time he seems to have decided that "systematic and extensive chemical and biological experiments should yield curative compounds." He realized that they must destroy, not by action from a distance, but only after fixation to the cells whose injury is wanted. The principle of chemotherapy seems first to have appeared at this time with the use of the terms "parasitotrophic vs. organotrophic." Then he voiced the opinion that the purely empiric approach had the chances heavily weighted against it, stating that there must be recourse to planned synthesis proceeding from substances with recognizable activity.

The first obvious manifestation of this conviction was a struggle with Bertheim to persuade that distinguished organic chemist to undertake a program of extensive investigation of atoxyl in an effort to achieve a therapeutic material for trypanosomiasis. Once more we are told little of what led Ehrlich to an interest in tropical disease. It is conceivable that the obviously parasitic nature of the etiologic microorganism might have been a factor. It is hard to see, however, why this would not have been equally the case with the tubercle bacillus of which he himself had been the victim—an organism which had occupied much of his attention and that of his beloved chief and inspiration, Koch. One is tempted to wonder whether once more the rising tide of German imperialism did not leave in the mind of this visionary character the conviction that those foreign lands essential to the economic expansion of his nation could be made habitable only if the diseases which then closed them to the white man could be eliminated. If this be true (and very little evidence to that effect exists), it implies a recognition by Ehrlich of the economic role of the scientist in public health.

From the development of trypan red and a demonstration of its effect on trypanosomes, the story is well known. It required only the demonstration by Schaudinn of the spirochete of syphilis, and the suggestion that it might be related to the trypanosome causing sleeping sickness, to lead Ehrlich and his co-workers to a study of the chemotherapy of syphilis. It is doubtful, however, that this would have succeeded had it not been for Hata, with his interminable Japanese patience, which gave him his perfected technique for inducing experimental syphilis. The period from the creation in 1906 of the Georg Speyer Haus, Ehrlich's new, privately financed laboratory, and the publication of the usefulness of salvarsan in 1911, is too well known to need com-

ment. Less recognized, however, is the period from 1911 to his death in 1915, during which time he was the butt of savage attacks from every side. It is now forgotten that then the cure for syphilis was regarded as "transcending God's law" and its discoverer was rated as an evil man. More than this, the skepticism of his scientific colleagues, and in many instances their bitter opposition, made depressing and tragic the ending to a useful and most productive life. It is interesting to note that salvarsan occasioned what was perhaps the first controversy concerning the patenting of a therapeutic agent. Ehrlich was reviled by many, despite the fact that he never received a cent in personal profit from the sale of this compound, and although he patented it for a very good reason —to insure the production of a safe, reliable drug.

In the light of modern knowledge, the tragic stress of Ehrlich's later years, consequent to the antagonism evoked by his almost miraculous contributions to medical science, was responsible for his death at the age of sixty-one.

Any individual and his activities are the product of his environment. This includes the conventions of his time, his physical surroundings, and, for the investigator, the total scientific picture of the day, composed of the available knowledge. Most important of all, however, are the individuals whose preceding or contemporary contributions make possible the accomplishments of a particular worker. In the case of Ehrlich, a unique scientific environment made possible the productive use of his particular talents.

It was sheer good fortune which brought this natively ingenious and brilliant mind, already fascinated by natural phenomena and emotionally swayed by color, under the influence of the great microscopist of the day, Waldeyer. Without the microscope to reveal the differential affinities of varied types of cells and their parts for different dyes, there would have been no basic principle of chemical specificity in biologic action as a basis for chemotherapy.

The microscope, however, was only a link in the chain, although its use was the foundation of the entire science of cytology and of cellular pathology, as developed by Virchow. It would have been only a feeble tool had it not been for Perkin and his discovery of aniline dyes upon which was based the entire German chemical industry. Contrast-staining of cells and tissues created not only pathology but also chemotherapy. The use of these dyes, however, was primarily the discovery

of Ehrlich's cousin, Weigert. There can be little doubt that this quiet, industrious man exerted a profound influence on Ehrlich as a young student. It is quite conceivable that without him, Ehrlich would have drifted into other areas of medicine.

The fourth factor essential to chemotherapy was knowledge of the bacterial etiology of disease, as developed by Pasteur and Koch. It is hard for us today to realize the completely revolutionary impact on medicine of the work of these two men. The ability to see clearly these causes of disease, by staining them and observing them through the microscope, provided a tool the strength and usefulness of which could not be ignored.

Not only did these several scientific developments influence Ehrlich's success; social factors were contributory also. It was a period of deep public interest in scientific matters, stimulated by the creation of a new German nation from a collection of minor states, strongly tinged with socialism, and with a vigorous system of governmentally controlled medical enterprise. Almost certainly some substantial part of this was due to the active political role of Virchow, the outstanding medical scientist of the preceding generation. Not only was the nation, through its government, vitally interested in medical science, but perhaps equally important, or more so, it was interested in the creation of institutes for specific purposes to solve certain well-defined problems of disease. The importance of this principle should not be overlooked. It represents the difference between the pursuit of science as an end in itself, and its pursuit to make an end to one or the other problem of society. It is the choice between these two points of view which still troubles the scientist and the society in which we live.

The completion of the total scientific picture which made Ehrlich's achievements possible came with the work of Roux, Yersin, and von Behring. They converted the study of bacteriology as an abstract science into an implement for the prevention and cure of disease. The specificity of immune reactions could only lead, in the mind of a scientist such as Ehrlich, observant of the chemical specificity of tissues and of the agents etiologic of disease, to the concept of chemical "magic bullets" for cure. The concept was inevitable, furthermore, from Lister's experiments on disinfection and Koch's thoughts on conversion of these to the principle of internal disinfection—which is nothing more nor less than chemotherapy.

When the name "Ehrlich" is mentioned, a mental image of the salvarsan therapy of syphilis is unavoidably created. Too frequently the fact is forgotten that this was only the end result of an immense number of individual, important scientific contributions. Every one of these, in turn, is consequent to the establishment of basic principles and new concepts of medical phenomena.

The first new concept developed by Ehrlich, and the one which pervaded his entire life work, was that of the fixation of dyes by biological units, cells or their parts, as providing an index of the constitution and function of these units. It is almost impossible to overestimate the importance of this point of view, which still provides the basis for much of modern medical investigation.

Perhaps the second outstanding principle he established was that of insistence upon the quantitative method. This was, of course, wholly understandable in an individual who was basically a chemist but by inclination working in biology. It is first seen in his employment of ricin in studies of antitoxin production, but it influenced the work of his entire life. He knew the absolutely essential nature of the reproducible experiment. Hata's ability regularly to induce experimental syphilis in the rabbit gave Ehrlich a yardstick which contributed almost as much to the discovery of salvarsan as did chemistry. Failure to employ an absolute index of therapeutic effect had caused Ehrlich to overlook an important discovery on one occasion, and this was a lesson he never forgot.

The third revolutionary concept was the one termed by him "athrepsia." He believed that agents active in a pharmacological sense exerted their effects by blocking those structural units of the affected cells which are normally employed for the ingestion of nutrients. This is obviously the understanding of what we know in modern terms as "anti-metabolite action." It has taken almost seventy-five years for this principle to be recognized as a basic one capable of being employed to achieve the most outstanding therapeutic results.

A fourth concept is that known as the "side chain theory." According to this theory, substances affecting cells were fixed by some anatomical part of the affected structure and in an effort to protect itself the cell produced not only more of these parts, but actually an excess, which it then sent into the bloodstream as antibodies. It is obvious now, and was obvious at that time, that such a simple morphologic concept could

not explain all the phenomena of disease. Nevertheless, it provided a perfectly useful means to explain the acquisition of resistance. Despite its failure in the overall scientific picture, it was the intellectual foundation of successful therapy.

Often forgotten is the prodigious conceptual contribution—the fifth made by Ehrlich—when he applied to diphtheria the principle of active immunity developed by Pasteur, and then converted it to a principle of treatment. Ehrlich's production of high-titer diphtheria antitoxin not only provided a therapeutic substance, it composed a basic cornerstone of specific treatment upon which was erected a whole fabric of scientific enterprise.

The term "cytochemistry" is conceived to be a modern one. Too often we forget that the earliest cytochemical experiments composed the sixth basic contribution of Ehrlich. They were concerned with the oxygen consumption of specific tissues, as investigated by what we now call "redox systems." Indophenol as a reagent is today on the shelf of practically every biochemical investigator; it was used by Ehrlich in 1880.

Vital staining as a principle—the seventh basic contribution of Ehrlich—was far more important than a technical procedure useful to the neuro-anatomist. It represented a concept that the chemical reactivity of cells and tissues in life might differ greatly from that manifested after death. This stimulated the conversion of pathology, the study of diseases from observations of the form in inert tissue, manifesting the alterations of past agents, to a study of the action of the agents themselves. Pathology is still undergoing this conversion.

Modern biochemistry, bringing with it our extensive knowledge of essential factors in nutrition, is today obvious and easily accepted. Anybody can understand pernicious anemia as a deficiency disease when it disappears almost overnight after the administration of vitamin B_{12} and folic acid. We fail to remember even the comparatively recent years of struggle over this concept. We also forget that it was Ehrlich who, almost seventy years ago, described the disease as a maturation defect and one due to the lack of some essential nutrient—his eighth contribution. His contributions to descriptive hematology were impressive, but medical science would have been far ahead had it heeded his dicta concerning etiologic mechanism.

The correlation of molecular configuration with biologic action

is a cardinal principle of modern pharmacology, and constitutes the ninth of Ehrlich's contributions. Few investigators interested in therapeusis would have the slightest doubt concerning its importance as a principle. Whereas it undoubtedly took its origin with Paracelsus and grew with a waning of Galenical doctrine, it is still too frequently overlooked.

As important as any other contribution of Ehrlich was his appreciation that investigation is not an end in itself. He employed chemistry to accomplish predetermined ends which were obviously important to society. His classic struggle with Bertheim exemplifies this principle. Atoxyl had been discarded as a therapeutic agent. Most investigators were prepared to throw up their hands and work in fields apparently more immediately productive. Ehrlich, however, constantly and intensively pleaded his case. Despite the conviction of the chemists that atoxyl could not be modified, he insisted that this could and must be done. Finally, by sheer persistence, he wore down the doctrinary prejudices of the erudite and thereby achieved a major therapeutic triumph. Although the triumph was important in itself, it is the principle involved—the useful employment of knowledge—which is the foundation of modern pharmacology, and his tenth contribution.

The dissemination of antibodies by way of maternal milk to nursing young is one of the cardinal tenets of modern immunology, and Ehrlich's eleventh contribution. Few recall or care about the enormous economic loss formerly imposed by diarrheal disease in newly born farm animals not permitted to nurse. Until Ehrlich's time, no one dreamed that immunity was not inherited on a genic basis and that suckling played any role. This has perhaps exerted an impact as great as any other one of Ehrlich's discoveries.

The "chemotherapeutic index" is a phrase today on the lips of all investigators concerned with specific treatment. Who remembers that it is simply a shortening and translation of Ehrlich's terms, "parasitotropic as compared with organotropic effects"—his twelfth contribution. In his day, and, indeed, in our day until recently, the field of medical science was permeated by skeptics who denied the ability of specific chemical compounds to exert different toxic effects upon different types of cells. The medical literature and the conversation of medical scientists from then to now have contained endless examples of pessimistic remarks to the effect that this or that biologic action cannot be exerted

without too great a generally toxic effect. This was said about trypanosomes until a therapeutic agent came to hand; about syphilis until salvarsan was discovered; about bacterial infections until we had sulfanilamide, penicillin and other compounds acting similarly; about malaria until the discovery of 4-amino-quinolines. It is still said about neoplastic cells, despite the availability today of compounds capable of effecting the cure of certain forms of transplanted cancer in experimental animals.

Every pharmacologist guides his endeavors along the principles of rates of absorption and excretion, of blood levels and the action of the metabolic products of administered drugs. As far as one can ascertain, these principles began with Ehrlich, and were his thirteenth great contribution. Certain it is that Ehrlich knew them well, and equally certain that he applied them. It is interesting and impressive to note that even today they must be constantly reiterated in any discussion of the usefulness of a biologic compound in therapy.

The concept of drug resistance as an acquired characteristic is presumably as old as knowledge of arsenic eaters. The ability of individual biologic units, such as bacterial cells, to emulate this accomplishment of the entire organism is overlooked with amazing frequency. This is despite the fact that the acquisition of bacterial resistance was described by Ehrlich, and more particularly despite the fact that a method for overcoming the tendency to resistance was demonstrated by him as his fourteenth contribution. Resistance is still evoked by the pessimists as a reason for not engaging in chemotherapeutic research. It is really incredible that the phrase "magna therapia sterilisans" can be so constantly forgotten. It required a major effort to understand that it applies to modern therapeutic research. Most important of all is the lesson to be learned from Ehrlich, that cell resistance does not negate the possibility of effective chemotherapy, but is simply a minor obstacle to be overcome.

It is in the cancer field that Ehrlich's fifteenth and last great fundamental concept perhaps most urgently requires application. It was Ehrlich who in an era of bacteriology recognized the cancer cell as the etiologic agent of the disease, cancer. He saw this cell, with crystal clarity, as the analogue of the invading bacterium, as the biological unit whose destruction must be accomplished if cure is to be achieved. It is incredible that today, directly in the face of the accumulated

experience of the past, we still find cancer research chiefly occupied with the examination of all kinds of biologic phenomena, on the assumption that the disease is some kind of mystery, only to be controlled if the nature of life itself is disclosed. One must presume from the record that if Ehrlich were here today he would proceed just as he did fifty years ago. He would seek the destruction of the cancer cell through the control of its ability to multiply, by bringing to bear upon it those adverse effects provided by immunology, by nature's own defense processes, and by the products of the chemist's creative ingenuity. Furthermore, he would not desist until he achieved his desired goal.

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THE DEVELOPMENT OF THE KNOWLEDGE OF THE LEUKOCYTE

An Exhibit Prepared for the 26th Annual Graduate Fortnight of The New York Academy of Medicine, on "Disorders of the Blood and the Blood-Forming Organs," October 19 to 30, 1953, Held in the Library Reading Room from October 19 through November 30, 1953

Little has been published on the development of knowledge of the leukocyte. An early book containing mention of the lmyphatic system is William Hewson's *Experimental inquiries; part the second* . . . London, 1774. The first description of the leukocyte is contained in William Addison's paper on "Colourless globules in the buffy coat of the blood," 1840. In the following decades, Donné, Craigie and Virchow made further contributions to this subject. In 1877 Paul Ehrlich was able to differentiate various forms of leukocytes with the help of his staining methods. These studies became the foundation of our present knowledge of these form elements. Since on search, no comprehensive bibliography on the history of the development of the leukocytes was to our knowledge available, an exhibit on this subject was felt to be desirable. We are listing for further reference the following titles:

HEWSON, WILLIAM (1739-1774). "Experimental inquiries: part the second . . ." London: 1774. First edition of this important work on the lymphatic system.

VELPEAU, ALFRED (1795-1867). "Sur la Résorption du pus et sur l'altération du sang dans les maladies. (Clinique de perfectionnement)," Revue Médicale, 1827, v.2, p.216. In 1827 Velpeau wrote of the peculiar alteration in the color of the blood, suggesting the admixture with it of "pus".

ADDISON, WILLIAM (1802-1881). "Colourless globules in the buffy coat of the blood," London Medical Gazette, 1840-41, v.27, p.479. In 1840 Addison made accurate observations on the white blood cells.

ANDRAL, GABRIEL (1797-1876). "Essai d'hématologie pathologique ou études des altérations principales du sang . . ." Bruxelles: 1843. A treatise on the analysis of the blood. Andral was the first to coin the term "anaemia".

DONNE, ALFRED (1801-1878). "Cours de microscopie complémentaire des études médicales, anatomie microscopique et physiologie des fluides de l'économie." Paris: 1844. The earliest microscopic recognition of leukemia. Donné attributed to the spleen the function of converting the white corpuscles into red corpuscles as William Hewson had done in the preceding century.

CRAIGIE, DAVID (1793-1866). "Case of disease of the spleen, in which death took place in consequence of the presence of purulent matter in the blood," Edin-

burgh Medical Journal, 1845, v.64, p.400. Description of an early case of leukemia.

VIRCHOW, RUDOLPH LUDWIG KARL (1821-1902). "Weisses Blut und Milztumoren," Medicinische Zeitung, 1846, v.14, no.34, p.157. In 1846 Virchow brought forward new evidence to support his contention that the abnormal cells of the blood in leukemia were really white blood cells and not pus cells as had been maintained by Craigie and John Hughes Bennett.

JONES, THOMAS WHARTON (1808-1891). "The blood-corpuscle considered in its different phases of development in the animal series." London: 1846. A description of the different types of blood cells in the blood of various animals and man.

VOGEL, JULIUS (1814-1880). "Ein fall von Leukämie mit Vergrösserung der Milz und Leber," Archiv für pathologische Anatomie und Physiologie und für klinische Medicin, 1851, v.3, p.570. In 1851, Vogel was the first German clinician to observe during life that there was a large proportion of abnormal colorless corpuscles in the blood of a patient in whom the liver and spleen were greatly enlarged.

WELCKER, HERMANN (1822-1897). "Blutkörperchenzählung und farbeprüfende Methode," Vierteljahrschrift für praktische Heilkunde, 1854, v.44, p.63. The earliest recorded leukocyte count was that performed by Hermann Welcker on Margaret Mueller on April 25, 1853.

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VIRCHOW, RUDOLPH LUDWIG KARL (1821-1902). "Die Cellularpathologie in ihrer Begrundung auf Physiologische und Pathologische Gewebelehre," Berlin: 1858. The first use of the word "leukocytosis"' to describe the condition in which the increased proportion of colorless corpuscles in the blood was dependent upon an affection of the lymphatic glands.

SCHULTZE, MAX (1825-1874). "Ein heizbarer Objecttische und seine Verwendung bei Untersuchungen des Blutes," Archiv für mikroskopische Anatomie, 1865, v.1, pl.2. In this work Schultze describes four forms of colorless corpuscles in human blood and recognized those which were finely and those which were coarsely granular. Number 7 is a polymorphonuclear cell, though some of the granules are large for those of a neutrophil.

NEUMANN, ERNST (1834-1918). "Ein Fall von Leukämie mit Erkrankung des Knochenmarkes," Archiv der Heilkunde, 1870, v.11, p.1. Neumann discovered the characteristic changes in the bone-marrow in leukemia and proposed the term myelogenous leukemia to distinguish it from the "splenic or lymphatic forms."

EHRLICH, PAUL (1854-1915). "Beiträge zur Kenntniss der Anilinfärbungen und ihrer Verwendung in der mikroskopischen Technik," Archiv für mikroskopische Anatomie, 1877, v.13, p.263. Erhlich's first paper on the staining of specific granulations in white blood corpuscles by means of aniline dyes was written while he was still a student.

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although it has been largely employed in France, and also in Germany, is almost unknown in clinical work in this country."

EHRLICH, PAUL (1854-1915). "Methodologische Beiträge zur Physiologie und Pathologie der verschiedenen Formen der Leukocyten," Zeitschrift für klinische Medicin, 1880, v.1, p.553. One of the greatest advances in modern hematology was the introduction of staining methods by Ehrlich whereby the various white blood cells could be readily recognized as belonging to the five varieties. An early paper on this subject.

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BROWN, THOMAS RICHARDSON (1872-1950). "Studies on trichinosis, with especial reference to the increase of the eosinophilic cells in the blood and muscle, the origin of these cells and their diagnostic importance," Journal of Experimental Medicine, 1898, v.3, pl.xxv. In 1898 Doctor Brown published a more detailed study.

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ROLLESTON, (SIR) HUMPHRY DAVY (1826-1944). "The history of haematology," Proceedings of the Royal Society of Medicine, July 1934, p.5, "As Professor William Bulloch told me some years ago, the word 'leucocyte' made its appearance first in 1855 in M. P. Littré and C. Robin's *Dictionnaire de Médecine* (Nysten); it was probably suggested by and derived from, the word 'leucocythémie' employed in 1851 by John Hughes Bennett in a paper read before the Société de biologie in Paris, to describe 'white-cell blood.' "

The portraits shown were:

GABRIEL ANDRAL, 1797-1876. Graduate of the Paris Faculty of Medicine in 1821, he was elected to the professorship of hygiene seven years later. In 1839, at the death of Francois Broussais, Andral succeeded him in the chair of pathology. His researches on the blood were among his more important contributions to medicine. He died in his seventy-ninth year.

PAUL EHRLICH, 1854-1915. Pioneer in the studies of morphology of blood, in tissue staining and immunology. Sir Humphrey Rolleston wrote in 1933: "Accurate knowledge of diseases of the blood-forming organs is an advance of the last fifty years, and is due to the stains introduced by Ehrlich in the seventies which enabled the greatly improved microscopes to show up the minute structure of the blood corpuscles."

SIR WILLIAM RICHARD GOWERS, 1845-1915. Born in London in 1845, he completed his medical training at University College, London, where he was a pupil of Sir William Jenner. Interested in diseases of the nervous system, his early contributions to medical literature dealt with the blood-vascular system. In 1880 he described for the first time the tract of nerve-fibers in the spinal cord, subsequently known as "Gowers's Tract." In 1883 he became physician and later, professor of clinical medicine at University College. He died in London in 1915.

ERNST HEINRICH PHILIPP AUGUST HAECKEL, 1834-1919. Laid the foundations of the theory of phagocytosis in 1882.

WILLIAM HEWSON, 1739-1774. A surgeon and anatomist, his researches on the blood were of great importance in establishing the essential character of the process of coagulation and the forms of the red corpuscles in different animals.

ELIE METCHNIKOFF, 1845-1916. The Russian physiologist whose recognition of the validity of the doctrine of phagocytosis in relation to wounds, disease,

immunity, and normal healthy life was the result of his scientific insight and boundless energy.

PIERRE CARL EDOUARD POTAIN, 1825-1901. Inventor of the blood-diluting pipette in 1867.

SIR HUMPHRY DAVY ROLLESTON, 1862-1944. A well-known pathologist in British medicine in the twentieth century. In 1922, his position as a leader of the medical profession in his country was recognized upon his election as President of the Royal College of Physicians.

FLORENCE RENA SABIN, 1871-1953. Born in Central City, Colorado. A graduate of Smith College and Johns Hopkins Medical School, she later became associate professor of anatomy and professor of histology—the first woman to become full professor at Johns Hopkins. Her studies in blood and blood diseases were among her principal achievements. She died at the age of 81.

WILLIAM SYDNEY THAYER, 1864-1932. "Thayer," said William H. Welch, "was the physician's physician. The world at large may have heard more of others, but to the medical élite—Thayer!" A graduate of Harvard Medical School in 1885, he later became Sir William Osler's assistant at Johns Hopkins Hospital and in 1905 professor of clinical medicine at the University. In 1917 he joined the Red Cross Mission to Russia to study general health conditions in that country. His researches on blood, malarial fever, parasitology, pellagra and cardiac disease were important contributions to the field of medicine. He died in 1932.

ALFRED ARMAND LOUIS MARIE VELPEAU, 1795-1867. A pupil of Bretonneau, he was surgeon to the Hôpital St. Antoine, La Pitié, and the Charité. He was professor of clinical surgery at the Paris Faculty from 1834 till his death in 1867. His great treatise on diseases of the breast was the most important work on the subject in its time.

RUDOLPH LUDWIG KARL VIRCHOW, 1821-1902. Born in Schievelbein in Pomerania, he took his medical degree in Berlin in 1843. From 1849 to 1856 his life was wholly devoted to work which led to the propounding of his theory of cellular pathology. He was director of the Berlin Pathological Institute until his death in 1902.

HERMANN WELCKER, 1822-1897. Born in Giessen, he took his medical degree in 1851 from the University of Bonn; he became assistant physician at the medical clinic in Giessen and later professor of anatomy. In 1876 he became Director of the Anatomical Institute there.

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SECTION ON MICROBIOLOGY*

Abstracts of Papers†

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The Lysis of Group A Streptococci by Extracellular Enzymes of Streptomyces Albus

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Enzymes capable of lysing a variety of bacteria are released by certain strains of Streptomyces albus in the course of sporulation of surface growths of this organism. Fractionation of these enzymes has been undertaken in connection with a study of their action on group A hemolytic streptococci. The major component of crude lytic filtrates is a proteolytic enzyme, but it has been found that purified preparations of this proteinase are unable to cause lysis of streptococci. The initiation of lysis is brought about by a second enzymatic component, present in relatively small amounts, which is without proteolytic action. The previously published evidence[1] concerning the separability of the proteolytic and streptolytic enzymes has been supplemented by fractionation experiments on partially purified material using zone electrophoresis. In veronal buffer at pH 9 on a supporting medium of potato starch, the proteinase behaves as a rather strongly basic protein which migrates with the principal protein peak. The streptolytic enzyme is less basic and is distinctly separated from the proteinase peak, although it appears to be a minor constituent of the total protein.

Studies of the mode of action of the streptolytic component indicate that the bacterial cell wall is the structure attacked by this enzyme. The findings with cell wall fractions prepared by grinding of dried streptococci in a ball mill[2] have been confirmed with cell walls isolated by the superior method of Salton[3] which he has applied to various species of bacteria. The identity of the cell wall preparations was established by electron microscopy. The streptococcal cell walls resist treatment with numerous solvents and a wide variety of enzymes, but are completely dissolved by the enzymes of Streptomyces albus.

The cell walls of group A streptococci, after removal of surface protein antigens with proteolytic enzymes, are composed chiefly of a carbohydrate-protein complex. The carbohydrate component, representing approximately two-thirds of the dry weight, is the group specific antigen (C carbohydrate) of the cell. It would appear, therefore, that the group specific antigen is localized in the cytoskeleton and serves as an integral part of this structure. It is composed of two monosaccharide components: rhamnose and N-acetyl glucosamine. The present evidence indicates that the streptolytic enzyme of Streptomyces attacks the carbohydrate of the cell wall, pos-

* Gregory Shwartzman, Chairman. Thomas P. Magill, Secretary.

† Manuscripts received July 1954.

sibly at some linkage involving the hexosamine.

The lytic enzyme has certain similarities to egg-white lysozyme and can probably be looked upon as an analogous enzyme with differing specificity. Salton[4] has demonstrated that lysozyme dissolves the isolated cell walls of Micrococcus lysodeikticus in the same manner that the Streptomyces enzyme lyses streptococcal cell walls. Other evidence indicates that here also the point of attack may be upon a hexosamine-containing carbohydrate.

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Lysozyme

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Fleming and Allison in 1922[1] applied the term lysozyme to a bacteriolytic agent or agents found widely distributed in nature. Although the wide distribution and the enzymatic nature of such agents had been reported before, Fleming was the first to make a systematic study of lysozyme. He introduced for the test of activity an organism very sensitive to lysozyme, Micrococcus lysodeikticus. Some strains of Sarcinae lutea have comparable sensitivities.

Thompson,[2] in his excellent review based in part on experimental work carried out jointly in his and my laboratory, defined lysozyme as a basic protein of low molecular weight, stable to heat in acid solution, which lysed certain microorganisms such as Sarcinae lutea and Micrococcus lysodeikticus. Meanwhile, this definition has become outdated and probably applies only to lysozyme of eggwhite and of mammalian fluids and tissues. The most notable exceptions to this definition are lysozymes occurring in the latex of many plants, especially of certain species of ficus, of hevea and papaya.[3] These plant lysozymes are heat labile and some are not basic proteins.

Our laboratory began the study of eggwhite lysozyme in 1933.[4] Its properties as a basic protein of low molecular weight were soon recognized.[5] Later the protein was crystallized and its mol. weight determined as approximately 15,000 and its isoelectric point as at pH 10.8.[6] It contains 2.5 per cent S, 8 per cent tryptophan and is free of phosphorus. Mammalian lysozyme appears to be similar, though not identical with eggwhite lysozyme. Smolens and Charney[7] obtained highly potent antisera in rabbits which inhibited eggwhite lysozyme, but not serum lysozyme.

The mechanism of lysozyme action has been explained by us[8] as depolymerization of a mucoid substance of the bacterial cell wall. This was confirmed by Epstein and Chain in 1939[9] and recently by Salton in Cambridge.[10] We still do not know the chemical nature of the lysozyme substrate. We do know that lysozymes of all sources hydrolyze a hexosaminidic bond contained in a mucopolysaccharide fraction or mucoid obtained from three different lysozyme susceptible microorganisms, M. lysodeikticus, Sarcinae lutea and Staphylococcus muscae. Such mucoid fractions were obtained by graded alkaline hydrolysis, removal of inert material and fractionation by alcohol.[11] The fractions had a nitrogen content of about 5 per cent and 20 to 30 per cent hexosamine, which was shown by isolation to be D-glucosamine.[12] These fractions formed very viscous aqueous solutions. The viscosity was rapidly and specifically lowered by lysozymes. On prolonged incubation, lysozymes hydrolyzed about one-third of the glucosaminidic bonds. No other reducing sugar, but N-acetylhexosamine, could be found in these hydrolysates. Lysozymes thus belong to a large group of enzymes, the glucosaminidases, a group to which also belong the different hyaluronidases and the chitinases.

The loss of viscosity of the substrate on incubation with lysozyme was utilized by us for a specific and sensitive determination of the enzyme.[11] With this method, lysozyme concentrations were determined in various tissue extracts and body fluids. In mammals, the highest lysozyme concentration was found in human tears and tear glands. Next highest are certain granulocytes, though little systematic work has been done with these cells. The concentration in the pyloric part of the stomach was also found to be very high.[13]

The finding of high lysozyme values in the pyloric region gave the impetus to our collaborative study, especially with Dr. John F. Prudden, on the possible connection of lysozyme with ulcerative alimentary disease,

* By invitation.

notably ulcerative colitis. It was found by our group and now confirmed by others that patients with chronic ulcerative colitis excrete in twenty-four hours over 150 times as much lysozyme as normal controls.[14] Furthermore, the lysozyme output faithfully reflected the clinical status of the patients. Patients with diarrhea of other origin had only slightly elevated lysozyme titers or at best showed only temporary elevations. The only exceptions were patients with regional enteritis who also had a chronically elevated lysozyme output. It was further shown by our group and later confirmed by others, that feeding of crystalline lysozyme in high doses led to ulcerative hemorrhagic lesions in dogs[15] and in other experimental animals.[16]

We suggested, on the basis of these experiments, that lysozyme was a causative agent in ulcerative colitis and in related diseases. Lysozyme in this concept was believed to attack the protective surface mucus of the digestive tract. However, no in vivo digestion of surface mucus could be demonstrated. A serious doubt in the causal relationship between lysozyme and ulcerative colitis was introduced by the finding of our group of high lysozyme titers in granulation tissue.[17] Later Gottschall[18] and Hiatt and their collaborators[19] and independently, Sammons in England,[20] reported that the fecal lysozyme was mainly contained in granulocytes. On the basis of these findings, most authors probably now consider the high lysozyme titer as an effect rather than a cause of the disease. This relationship naturally does not account for the ulcerative action of lysozyme when applied locally to the mucosa and requires further studies.

What is the biological function of lysozyme? With Fleming, most authors assumed lysozyme to function as a defence against bacterial invasion. Indeed, the high concentration of the enzyme in tears and in leukocytes speaks for such a role. However, apparently only man has a high titer in tear glands. Furthermore, the organisms most susceptible to lysozyme are harmless saprophytes. Some microorganisms contain lysozyme, among them are some which are themselves susceptible to lysozyme such as sarcinae. As mentioned earlier, the latex of many plants contains lysozymes in concentrations many times those found in egg-white, the richest source in animals. Only a few species of birds' eggs, however, have high titers of the enzyme. These facts may point to a metabolic role of lysozyme. In fact, the known lysozymes appear to belong to the large group of glucosaminidases. Undoubtedly more information will be forthcoming on the role, the specificities and the possible lytic actions when this group of enzymes will be studied systematically.

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Bacterial Collagenases

JOHN D. MACLENNAN*

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Of the many unusual properties of collagen, one of the most striking is its great resistance to all the commoner proteolytic enzymes. Indeed until recently, the only biological materials known to have collagenolytic powers were certain vegetable and plant extracts such as papain or ficin. Subsequently maggots were found to possess this property, but a big advance was made by the discovery that certain bacteria could also produce collagenases, sometimes in very large amounts. Today, three and probably four species are known to secrete such agents: two of these are Clostridia—Cl. perfringens and Cl. histolyticum; one is an aerobic spore bearer of the Subtilis group, and the fourth is Vibrio cholerae. By far the most active producers of collagenase are the two anaerobes and it is with our work with these organisms that I shall deal tonight.

At once it can be said that, from a biochemical point of view, we know considerably more about the Perfringens enzyme. The reason for this is quite simple—it has been obtained (particularly by Van Heyningen at Oxford) in relative purity, whereas the most that can be said about the Histolyticum preparations is that although they are highly active, even the best of them are certainly contaminated by other proteolytic enzymes. I shall return to this point later.

To get back to the Perfringens collagenase, this question of purity is, of course, only relative and I want to make it quite clear that Van Heyningen did not obtain this enzyme in the crystalline form—his best preparations were probably 50 per cent pure and appeared to be free of any other enzymic activity known to exist in Perfringens filtrates. However, I should add that from our own experience, I think it probable that many, if not all of these preparations did have traces of other proteinases present. But I doubt if this fact seriously invalidates the broad outline of his findings.

There is little point in going into the general properties of this enzyme in any detail, for there is nothing unusual about them. It is active optimally in the range pH 7.0 to 7.5 and does not appear to require any very special activation system; nor apart from certain heavy metals, is it readily inhibited. Aside from the primary fact of being able to attack fresh unaltered collagen, the most interesting property of the enzyme is its extremely narrow substrate specificity, i.e., it can hydrolyze only fresh collagen, denatured collagen (in the form of hide powder) and gelatin. It has no activity on a vast number of other proteins, including urea-denatured hemoglobin, casein, horse-serum (natural and urea-treated), serum albumin, or even so simple a protein as clupein. Nor were such synthetic analogues as glycylproline, carbobenzoxy-prolyl-glycine, o-acetyl-hydroxyproline in any way affected.

Unfortunately, Van Heyningen did no qualitative studies on the end-products of collagen hydrolysis with his most highly purified preparation. It is, however, known that NH_2 and COOH groups are liberated.

So much for the Perfringens collagenase. However, I do feel I ought to emphasize that the bulk of the observations which I have quoted are Van Heyningen's and not ours. When MacFarlane and I first picked up this enzyme in 1944, we were working in N. W. Europe and did not have the facilities to carry our study too far, so we handed our preliminary findings over to Van Heyningen. Later on, when I came back to the collagenases, I soon found that Histolyticum was a much better producer of the enzyme and it is the results of our studies with this organism that I should now like to discuss. Unhappily, we have not been nearly so successful as Van Heyningen and, as I have said, the position to date is much less satisfactory.

* By invitation.

Quite early in our work, we were able to identify and get out in a fairly pure form, a trypsin-like proteinase—distinct from the cysteine activatable one recently reported on by Lepow, Pillemer and others—which is not cysteine activated. The only point I really want to make about these enzymes is that they are without any collagenase activity, although they will, of course, readily digest denatured collagen and gelatin in addition to a large number of other protein substrates.

The difficulty arises in the fact that we have, so far, been quite unable to obtain any collagenase preparations which are free of proteinase. I shall not weary you by listing the description of all the methods we have employed. All have been uniformly failures. In other words, as we remove proteinase from our filtrates, the collagenase activity also disappears.

Because of these repeated failures, we began to wonder whether the collagenase may not be a proteolytic enzyme in the strict sense of the word, but act rather as a depolymerase or "denaturase" whose action is merely to render the collagen molecule more accessible to the proteinases. And for this very nebulous hypothesis, we have recently got a little rather nebulous confirmation.

I should, however, like to add that incidental to these studies, we have discovered in many of our preparations the entirely unsuspected presence of no less than three other enzymes, none of which will attack even denatured collagen. These are:

1. A tripeptidase which splits leucyl-glycyl-glycine to glycyl-glycine and leucine and is inhibited by cysteine.

2. A dipeptidase which splits leucyl-glycine to leucine and glycine. This required cobalt activation. Manganese has a slight activity in this respect, and once again cysteine inhibits.

3. An enzyme which attacks benzoyl-arginine amide and arginine-methyl-ester. This is very markedly cysteine activated.

What part, if any, these new enzymes play in the collagenolytic process remains to be determined.

One point which is probably worth mentioning here, is the influence of hyaluronidase on the lytic process. As you all know muco-polysaccharides seem to play some role in the structure of collagen—for instance the addition of such substances to collagen preparations can markedly alter the periodicity of the banding. I am certainly not competent to judge the significance of these findings, but recently Johnson in England has reported that treatment with hyaluronidase markedly changed the physical character of collagen, namely, there was an increase in swelling and in solubility in acid, together with a decrease in shrinkage-temperature. It has been suggested on several occasions that the collagenase is really some sort of muco-polysaccharidase. Well, we repeatedly failed to detect any hyaluronidase either in the filtrate or in our preparations. And Dr. Karl Meyer, I am happy to say, has not only confirmed these findings so far as hyaluronic acid is concerned but has extended them to include chondroitin sulfate A and B.

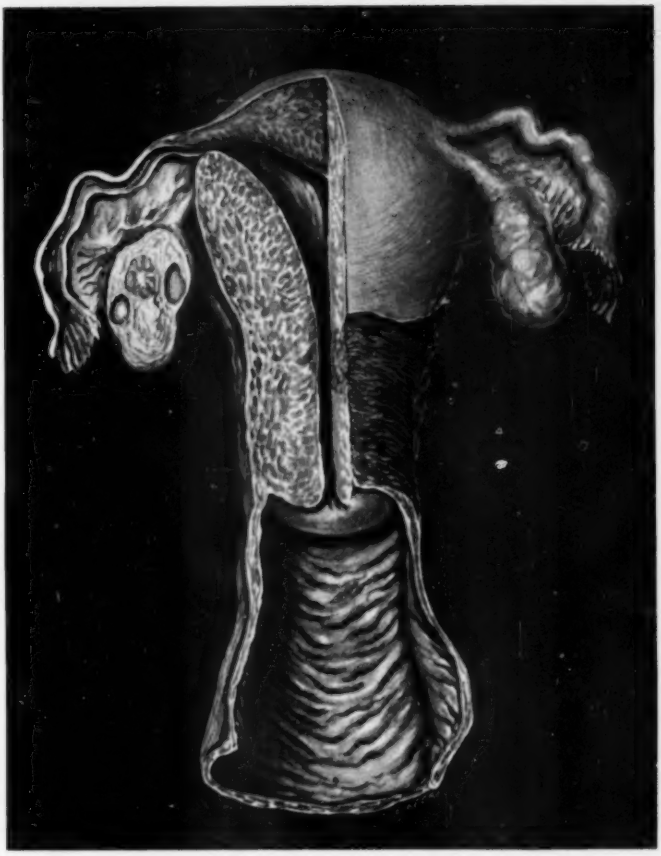
Nor does the addition of bull-testis hyaluronidase to the collagen suspension render it susceptible to digestion by proteinases.

Because of the impurity of our preparations, I do not think there would be much point in describing our studies on the end-products of the enzymic hydrolysis of collagen. I should, however, like to show you the sort of thing the collagenase does to the collagen fibril. These electron micrographs I owe to Dr. Gross of M.I.T.

One last point that I think is worth mentioning is that in virtue presumably of the collagenase, even our impure preparations have an extraordinarily high specificity in vivo. The proteinases, I may say, have no obvious effect on injection in the animal body, whereas the collagenase preparation selectively digests collagen and, in consequence produces a variety of very interesting and bizarre lesions. Because of this, I believe that the enzyme or enzyme system may well prove to be a tool of considerable value in various fields of biological research. And, in fact, we are now receiving many more requests for material than we can possibly fulfill.

And that really is about all. As you see, we have not really got very far. The field is wide open and quite frankly I should be most grateful for any criticisms or suggestions.†

† Since the above paper was given, we have succeeded in obtaining preparations of Cl. histolyticum collagenase which are free of the proteinases.



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In clinical evaluation, covering a period of two and one-half years, Vallestril was found* to be "an effective synthetic estrogen . . . singularly free from toxic effects and complications, especially uterine bleeding. . . . The beneficial effect of the medication appeared within three or four days in most menopausal patients . . . . failure to encounter withdrawal bleeding in any patient was most gratifying. . . ."

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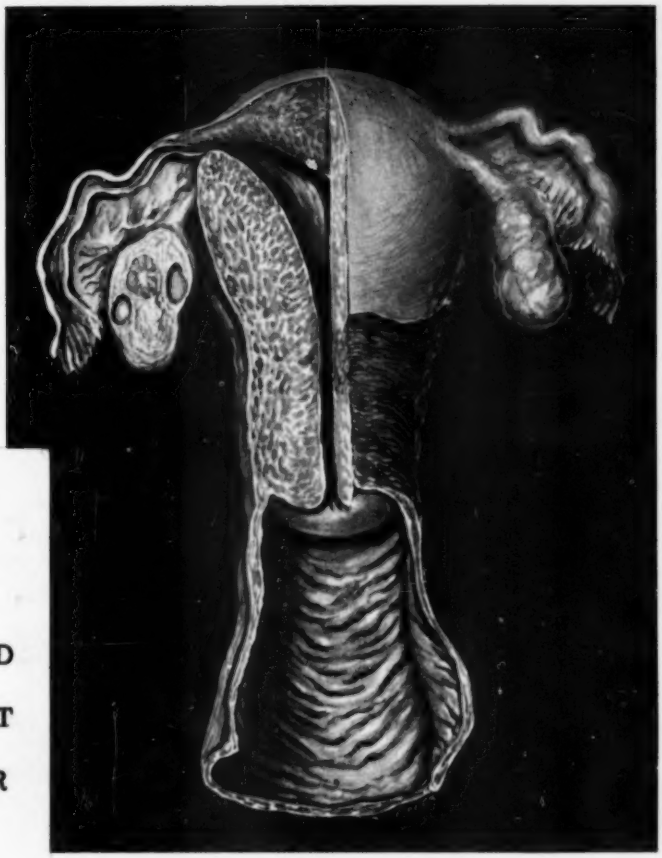

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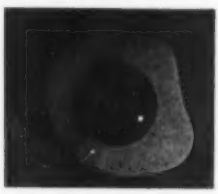

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DOSAGE: The usual dose of Theominal R.S. is 1 tablet two or three times daily. When improvement has been maintained for a time, the dose may be reduced or medication suspended occasionally until its resumption is indicated.

HOW SUPPLIED: Theominal R.S. is supplied in bottles of 100 tablets.

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1. Werner, A.: Acta endocrinol. *13*:87, 1953.
2. Malleson, J.: Lancet *2*:158 (July 25) 1953.
3. Goldzieher, M. A., and Goldzieher, J. W.: Endocrine Treatment in General Practice, New York, Springer Publishing Company, Inc., 1953, p. 23.

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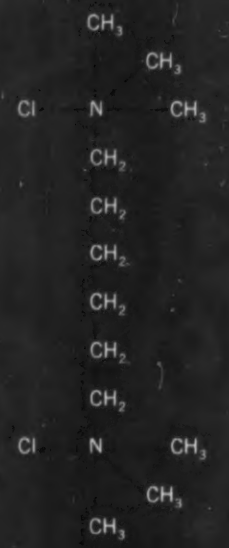

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1. Ford, R. V., and Moyer, J. H.: Am. Heart J. *46*:754 (Nov.) 1953.

2. Crawley, C. J., *et al.*: New York State J. Med. *54*:2205 (Aug. 1) 1954.

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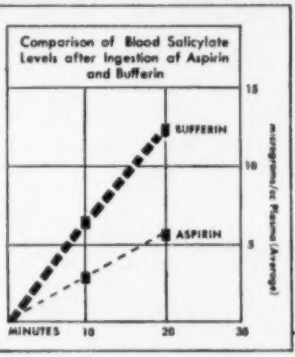

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1. Effect of Buffering Agents on Absorption of Acetylsalicylic Acid. J. Am. Pharm. Assoc., Sc. Ed. 39:21, Jan. 1950
2. Gastric Tolerance for Aspirin and Buffered Aspirin. Ind. Med. 20:480, Oct. 1951

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